ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF

INTERNAL SECRETIONS

Volume 16, Number 4 JULY-AUGUST, 1932 Serial No. 84

LAURENCF-MOON-BIEDL SYNDROME*

WILLIAM ANTHONY REILLY, A.B., M.D.
AND
HANS LISSER, A.B., M.D.
From the Departments of Pediatrics and Medicine and the Ductless Gland Clinic of the University of California Medical School

The Laurence-Moon-Biedl syndrome is uncommon. It is characterized by dystrophia adiposogenitalis, atypical retinitis pigmentosa, mental deficiency, familial occurrence and skeletal abnormalities, most frequently polydactylism and syndactylism.

Including the four cases reported below, 77 instances of this rare malady have accumulated in the literature since Laurence and Moon first reported four out of a family of eight children, in the British Ophthalmalogical Review, 66 years ago (1866).**

Biedl in 1922 and Raab in 1924 reported another family of six living boys and girls of healthy parents, two of whom (a brother and a sister) showed atypical retinitis pigmentosa, adiposity, genital dystrophy, polydactylism and mental deficiency. Two others in the family, who died in infancy, showed polydactylism. Assuming that these might also have developed the full syndrome had they lived, here would have been another instance of four afflicted in a family of eight children. Solis-Cohen and Weiss in 1925 and Ricaldoni and Isola in 1928 likewise reported four patients affected in a family of eight children. This constitutes a bizarre parallelism, namely, three familes of eight children each, four in each family, afflicted with this peculiar disease.

This syndrome also occurred in half of the offspring of the families reported by Madigan and Moore, Rosenstein, Zondek, Beck, McKinney, Ornsteen, McCrae and Weiss, also in one-third of the offspring in the families of DeCyon, Grossman, Rozabal-Farnes, and Bing, and in all the children in the families reported by Kruckmann and Meyer, and Bernhardt.

In the appended table are listed all the cases the authors have been able to find after a most painstaking search of the literature. In this table

*Read before The San Francisco County Medical Society, October 6, 1931.

**Jonathan Hutchinson re-examined this family 10 years later, 2 more children having been born in the meantime. These latter were not afflicted with the disease, so that the incidence in this family is 4 out of 10, rather than 4 out of 8.

the author's name is given with the year of publication, number of children affected in each family, the presence or absence of retinitis pigmentosa, obesity, genital dystrophy, mental retardation, polydactylism or other skeletal abnormalities, also a note as to the therapy attempted and its effect, and miscellaneous remarks.

A comparison of the bibliography with the table of cases reveals discrepancies which are to be accounted for in the following manner. In one instance the same patient has been reported twice (Chaillou's case was reported by Bardet); or an author refers to a case reported by someone else which, on consulting the original article, did not, in the opinion of the writers, represent even a partial example of this syndrome. (Thus S. Hansen quoted by Boenheim.) Finally the data on Borchardt's case were inaccessible by direct reference or quotation.

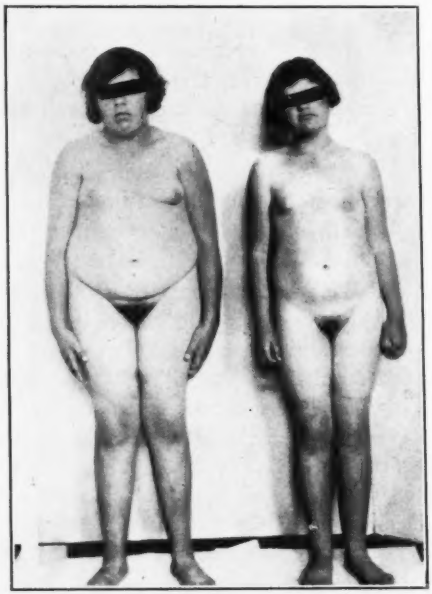


Fig. 1.—Patients described in the text: "E. C." on the left, "J. C." on the right.

CASE REPORTS

Two of the patients to be reported are sisters, aged 11 and 13 years, of Italian parentage. The mother, aged 33 years, father aged 44 years, two brothers, 18 and 8 years respectively and one other sister aged 16 years, were all living and well. These five children are the only progeny; there were neither dead children nor any miscarriages.

Special inquiry failed to reveal any hereditary factors such as obesity, blindness, skeletal defects, mental, endocrine or luetic disease.

CASE 1, E. C., University of California Hospital Out-Patient Department No. 200,127, aged 13 years. Birth and development during infancy were apparently normal. The only disease reported was a mild case of measles at 3 years of age. Because of occasional sore throats the tonsils were removed at 8 years. Menstruation had just begun.

The patient had always been obese. Mental retardation was first noted on entering school at 6 years. Impairment of vision attracted attention at 9 years of age. Vision diminished progressively and the patient was almost totally blind when first seen. There have been no symptoms of increased intracranial pressure. Painless progressive dorsal kyphosis first appeared at 10 years of age. At this time the patient was seen at the Stanford University Medical School Clinic and the syndrome recognized, but the case was not published.

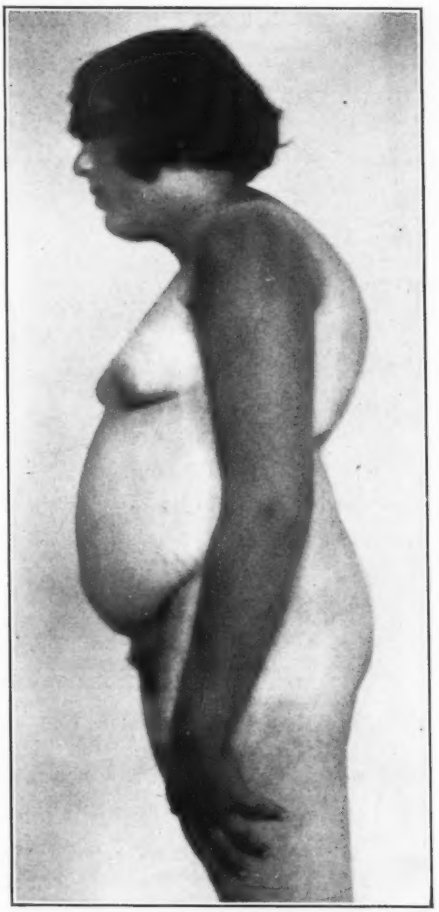


Fig. 2.—"E. C." showing the marked kyphos.

Our examination disclosed a large, heavy, dull girl utterly lacking in animation. The obesity was somewhat generalized but predominately of the girdle or so-called hypopituitary type (see figures 1, 2 and 3). The hair was profuse but not coarse and dry and there was no abnormal distribution. Racial pigment existed in a slightly coarse skin but there were no myxoedematous infiltrations. The tongue was thick and large and the teeth not remarkable. Her tapering, slightly thick fingers were suggestive of the hypopituitary hand. The secondary sexual characteristics were well developed. Despite the kyphos, her height was 61 inches, span 66 inches, lower measurement 33 inches and upper measurement

28 inches. Her weight, 175 pounds, was about 70 pounds over the ideal weight for height and age.

Her eyes deserve special comment. The conjunctivae, sclerae and pupils were normal. There was a mild bilateral rotatory and lateral nystagmus with a left external strabismus. The right fundus had diffuse vitreous hemorrhages with an old retinal detachment below, on the nasal side. On the retina were several areas of white exudate and many splotches of pigmentary infiltrations. The globe tension was minus one. The left fundus showed the same vitreous hemorrhages; a torn retina was detached in the upper outer portion. There were many blotchy pigmentary infiltrations in the retina; the disc was pale. The globe tension was decreased.

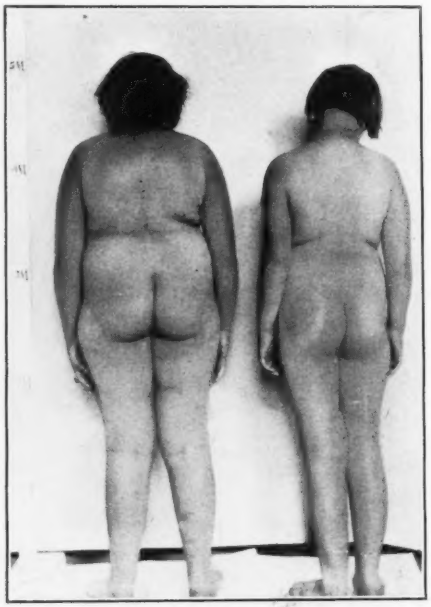


Fig. 3.—"E. C." and "J. C." patients 1 and 2.

The thorax showed marked dorsal kyphos (see figure 2) from the 5th to the 10th dorsal vertebrae and this region was almost immobile. There was a marked lumbar lordosis with good motion. There were neither supernumerary toes, fingers nor webbing.

The heart and lungs were normal; blood pressure was 122/82 and the pulse and temperature were never subnormal. The abdominal and neurological examinations and the external genitalia were normal.

Roentgenograms of the thoracic vertebrae showed that the 5th to the 10th were markedly irregular in outline and the bodies showed some rarefaction and partial collapse. The intervertebral discs were more narrow than normal and there was a left scoliosis. These findings were interpreted as an osteochondritis deformans juvenalis dorsi. Roentgenograms to determine the bone age revealed an ossification status of 16 to 17 years as compared with a chronological age of 13 years. The sella turcica was slightly enlarged but not deformed. There was no roentgenographic evidence of supernumerary finger or toe buds.

Routine blood and urinalysis were normal. The blood Wassermann reaction was negative. The fasting blood sugar was 66 mgm. per cent. The spinal fluid showed normal pressure, no cells, negative Pandy and Wassermann reactions. The basal metabolic rate was 21.0 per cent minus. The intelligence quotient, 44 per cent, was in the range of a high grade imbecile.

CASE 2, J. C., University of California Hospital Out-Patient Department No. 200,128, aged 11 years, sister of Case 1. This girl had had mild torticollis since birth and also queer aimless body and limb motions up to 3 years of age. She did not walk until 3 years of age. Her gait was reported as incoordinate for 3 years. Apparently she had been obese most of her life.

Upon entering school at 6 years of age mental retardation was noted and for the past year her school work had been very unsatisfactory. A visual failure was first noticed 6 months ago and at present she has her greatest difficulty at night.

This child resembled her sister in obesity, hair, skin and fingers (see figures 1 and 3); however, the purposeless motions and incoordinate gait were not in evidence. She had well developed secondary sexual characteristics but menses had not appeared. Her height was 58½ inches, the span was 55 inches, the upper measurement 29 inches and the lower measurement 29½ inches. Her weight, 117 pounds, was about 30 pounds more than the ideal weight for her height and age.

There was a moderate kyphosis from the 2nd to the 5th dorsal vertebrae and motion here was slightly decreased. There was no supernumerary fingers or toes.

A slight left internal strabismus was present in the left eye. Both eyes showed rotatory nystagmus. Both fundi revealed diffuse splotchy pigmentary infiltrations of the retinae; the discs appeared normal. Vision was diminished but due to lack of cooperation exact objective measurement was not obtainable. The ophthalmalogist diagnosed the condition as atypical retinitis pigmentosa.

At Stanford Hospital in 1928 her urine, blood count and Wassermann were negative. An intelligence quotient was 36 per cent.

Further data were unobtainable since the family lived some distance from San Francisco and could not afford to return.

Both children have taken thyroid extract gr. IV to V and whole pituitary extract gr. XV to XX daily for 8 months. The older girl lost 45 pounds and is much more active, alert and interested in her surroundings. Most remarkable is the fact that she can see much better than before. She can now attend to her wants, walks around the house, and plays in the yard unattended whereas before she required constant attention. She now reads her younger sister's school books for the first time.

This patient's fundi showed reattachment of the retina, resorption of old hemorrhage and full visualization of disc heads, a change which followed the glandular therapy, and presumably can be attributed to it.

The younger sister lost 20 pounds in weight, was much more alert and had not retrogressed mentally. Though the mother insisted that her vision was improved the ophthalmalogist could not detect any objective improvement as the child's mentality prevented cooperation. However, her vision was not progressively failing as it had been before the therapy.

Immediately before the manuscript of this report was submitted for publication, the patients, E. C. and J. C., were re-examined. At this time, 11 months after treatment was started, E. C. had complete retinal detachment and total blindness in the left eye. Vision in the right eye was about the same as at 8 months after therapy was started. The patient still could care for herself, was fairly animated, weight had not increased over 140 pounds and experience had shown that if therapy was stopped there was a noticeable relapse in about 10 days. Only two menstruations had occurred in 11 months. J. C. had grown 2 inches in one year and lost 20 pounds. Her status was the same as at 8 months. However, her mentality was not improving and she was promoted from the third grade only because of her size and the extra time spent in that grade.

We are also reporting two additional patients who, while atypical, have some of the pathognomic findings.

CASE 3, M. W., 11 years of age, American, female, was congenitally blind, obese and slightly retarded mentally. There was no definite genital dystrophy nor polydactylism. As she was an adopted child her family history was unknown to her foster parents. Significantly, her retinae showed some pigmentary clumping.

CASE 4, E. B., 19 years of age, American, female, (see figure 4) had visual deficiency following a questionable sinus infection during the 12th year. She was short in height, slightly obese, did not menstruate until after her 15th year. There was no polydactyly nor mental retardation. Her fundi showed a choroid

retinitis but the ophthalmalogist thought atypical retinitis pigmentosa was present also due to clumped pigment.

These two patients have been classed as doubtful cases. Further findings are recorded in the appended table.

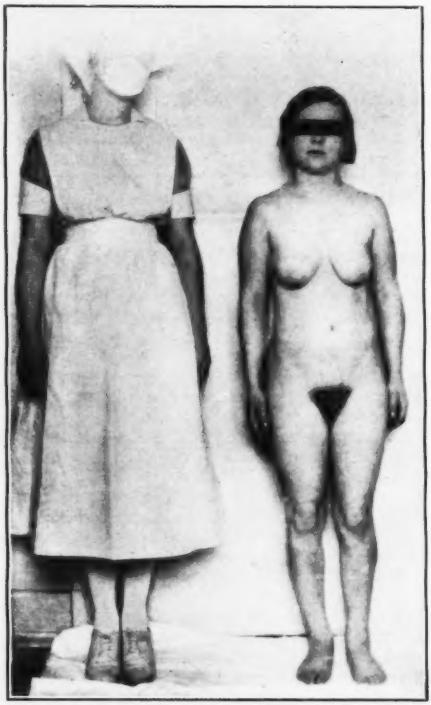


Fig. 4.—"E. B.," 19 years of age, with a normal sized woman of same age, to show stunted growth.

ETIOLOGY

The etiological factors underlying this extraordinary malady remain obscure. Indeed all theories as to its causation will continue to be purely speculative until some of these cases are studied at autopsy. The one autopsy, Bauer's, yielded nothing characteristic. Some writers have been inclined to implicate the hypophysis, partly because of the dystrophia adiposogenitalis element in the syndrome and partly because of the asserted improvement from pituitary organotherapy. Other writers have leaned toward a cerebral origin involving the postulated genitrophic centers in the hypothalamus. Others would link these two possibilities by assuming on the one hand a defective pituitary secretion, or obstructions or inflammations interfering with the fibers connecting the hypophysis via its stalk with the floor of the third ventricle and hypothalamus; or again, on the other hand, one might predicate congenitally defective genitrophic centers which are therefore unable to react to a normal hypophyseal secretion. However this may be, it must be admitted that in the light of our present

knowledge, hypophyseal, and/or, hypothalamus disease fail to explain the almost invariable association of atypical retinitis pigmentosa, and/or, skeletal abnormalities such as polydactylism. The latter, most certainly, necessitates the assumption of a congenital influence, and the almost invariable familial occurrence demands consideration of peculiarities in hereditary germ cells themselves.

SYMPTOMATOLOGY AND DIAGNOSIS

One of the writers (W. A. R.) deems it advisable to emphasize that each article listed in the bibliography was read in the original with only one exception. (F. Schweitzer's case, quoted from Madigan and Moore; the original paper appeared in an Argentinian pediatric journal which could not be obtained in the United States.) Although the great majority of references were obtained in the University of California Medical School Library, the courteous cooperation of the Lane Medical Library, San Francisco, The New York Academy of Medicine and the Surgeon's General Library in Washington, D. C., is gratefully acknowledged.

The symptomatology and differential diagnosis require no elaboration since the odd association of dystrophia adiposogenitalis, mental retardation, retinitis pigmentosa, familial occurrence, and polydactylism render the diagnosis obvious. However, it should be stated that the six cardinal symptoms—namely, (1) obesity, (2) genital dystrophy, (3) retinitis pigmentosa, (4) mental deficiency, (5) polydactylism and (6) familial occurrence—are by no means all invariably present. There are a number of cases in which the classical syndrome is completely represented. But a greater number of instances occur in which one or more of the characteristic symptoms are absent and in consequence it should be understood that partial clinical combinations or subtypes require recognition. For example, one may encounter (1) obesity, genital dystrophy, retinitis pigmentosa; (2) obesity (but without genital disturbance), mental deficiency, retinitis pigmentosa; (3) retinitis, polydactylism. Other groupings are conceivable, but, unless the classical syndrome is present in toto, a "*sine qua non*" for the diagnosis of Laurence-Biedl disease necessitates familial occurrence.

In the reported cases there are 25 with the complete findings (retinitis pigmentosa, dystrophia adiposogenitalis, polydactylism, mental deficiency and usually familial occurrence); also an additional 10 who were questionably complete cases. Partial cases having either retinitis or polydactylism number 26 with one additional questionable case. All others, 15, are doubtful.

Summary of the findings tabulated in the appended table reveals the following data:

Thirty-nine were below 15 years, 25 over 16 years and in 12 the age was not mentioned.

Thirty-two were males, 38 females and in 7 the sex was not referred to.

TABLE OF REPORTED CASES

Case No.	Year	Author	Age	Sex	Children in Family	Race	Adiposity	Atypical Retinitis Pigmentosa	Polydactyly
1	1866	J. C. Laurence R. C. Moon	7	F	10—Cases 1–4 related	English	Yes	Yes; visual defect for 2 yrs.; hypermetropy, strabismus, nystagmus	Yes
2	1866	J. C. Laurence R. C. Moon	20	M	10	English	? Yes	Yes; visual defect from earliest years; strabismus, hypermetropy, nystagmus	No
3	1866	J. C. Laurence R. C. Moon	18	M	10	English	Yes	Yes, visual defect for 6½ yrs.; hypermetropy, strabismus, nystagmus	No
4	1866	J. C. Laurence R. C. Moon	15	M	10	English	? Yes	Yes; visual defect for 3 yrs.; hypermetropy, strabismus, nystagmus	No
5	1898	DeCyon	12	M	3—two brothers each had 12 toes		Yes	Not stated; ptosis, myosis, nystagmus	12 toes
6	1908	Grossman	Adult	M	One brother had polydactyly, faulty vision, congenital heart; one brother had normal vision and congenital heart	Austrian	Yes	Yes; hemeralopia began at 15 yrs.	11 fingers 12 toes
7	1908	Kruckmann & Meyer	15	M	2—brother of Case 8	German	Yes	Yes; visual defect at 8 yrs., nystagmus	No
8	1908	Kruckmann & Meyer	9	F	2	German	Yes	Yes	No
9	1912	Von Jaksch	14	M	Not stated	Not stated	Yes; since 5 yrs.	Yes; visual defect after meningitis at 3 yrs.	11 fingers
10	1913	Bertolotti	39	F	4—living and well	Italian	Yes	Yes; visual loss since infancy; optic atrophy, divergent strabismus and nystagmus	11 fingers 12 toes
11	1913	Rozabal Farnes	11	M	6—brother of Case 12	Spanish	Yes	No; "hemianopsia (bitemporal); atrophy of temporal side of nerve head"	12 toes
12	1913	Rozabal Farnes	14	M	6—brother of Case 11	Spanish	Yes	No; optic atrophy with nearly complete blindness which began at 3 yrs.	12 toes
13	1917	F. Schweitzer (copied from article by J. J. Madigan & T. V. Moore)	16	M	Not stated		Yes	Disseminated choroiditis; optic atrophy	Not stated
14	1918	J. J. Madigan & T. V. Moore	10	M	2		? Yes	Yes; optic atrophy, nystagmus	No
15	1920	G. Bardet	4	F		? French	Yes	None found at age 4 yrs., but at aet. 10; visual defect at 3½ yrs.; also choroid retinitis; divergent left strabismus	6 toes on right foot

OF LAURENCE-BIEDL SYNDROME

Genital Dystrophy	Mental Deficiency	Sella Turcica	Basal Metab. Rate	Therapy	Result	Miscellaneous Notes	Characteristic Complete Syndrome	Partial Syndrome	Doubtful Cases
Yes; at act. 16 yrs. Hutchinson reports no menses	Yes					Father and mother normal physically including fundi		Yes	
Yes; penis size of year old						Short for age, 63¼ ins., slouchy, helpless, slow gait, lumbar lordosis		Yes	
Yes; genitals of 5 yr. child	? Yes					Short for age, 54 ins., slouchy, helpless gait		Yes	
Yes, as in 20 yr. brother	Yes					Short for age, 53¼ ins., slouchy, helpless gait; all three males in this family became paraplegic 10 yrs. later. (Hutchinson)		Yes	
	Yes			Iodothyroine and strychnine for 2 mos.; hypophysine for 3 weeks	Lost 12 lbs. Lost 15 lbs. and became more active	Acromegalic features		Yes	
No	No					Microcephaly; congenital heart		Yes	
Yes	Slightly defective	Normal						Yes	
Yes	Not mentioned	Normal				No mental deficiency mentioned		Yes	
Yes	? Yes	Normal		Pituitary ext. for very short time	Not stated	Wassermann negative; no consanguinity	? Yes		
Yes; external genitalia infantile	Yes	Increased depth, clinoid spread apart, erosion in the post. clinoids; tumor suspected supra and retro sellar		? Thyroid and pituitary ext.	Without effect	Wassermann negative; increased carbohydrate tolerance; dental and other bony anomalies; brachy and microcephaly short for age, 55 ins.	Yes		
Yes		Deepened		Operation refused; no opotherapy		Hypophyseal tumor diagnosed hypospadia		Yes	
Yes		Deepened		Same as Case 11		Both brothers had negative Wassermanns; short for age, 47 ins.		Yes	
Yes		Enlarged		Mercury; pituitary ext.	Not stated	Classified by author as Frohlich's syndrome; Wassermann negative; no glycosuria			Yes
Yes	Yes	Flattened; post. clinoids destroyed; ante. clinoids pressed down; suprasellar tumor suspected				Marked polydipsia; no polyuria; mild microcephaly; many defects in mother's paternal relatives		Yes	
	? Yes	Normal		Pituitary and thyroid ext.	Loss of weight	Dorsal Pott's Disease appeared at age 11; Wassermanns of patient and mother negative	? Yes		

TABLE OF REPORTED CASES OF

Case No.	Year	Author	Age	Sex	Children in Family	Race	Adiposity	Atypical Retinitis Pigmentosa	Polydactyly
16	1920	Variot & Bouquier	15 mos.	F	1	? French	Slight	Fundi not examined	Poly. and syndactylism of all extremities
17	1920	S. Hansen ?							
18	1922 and 1924	A. Biedl & W. Raab	22	F	8—sister of Case 19 two other children had polydactyly		Yes	Yes; poor vision since infancy; strabismus, postcortical cataract; limited visual fields	Yes with syndactylism
19	1922 and 1924	A. Biedl & W. Raab	16	M	8		Yes	Yes; postcortical cataract; contracted fields	12 fingers 12 toes
20	1922 and 1924	A. Biedl & W. Raab	13	M			Yes	Yes; narrow visual fields	No
21 22 23	1922	Meissner					Yes	Yes; choroid retinitis with ? lues	Not stated
24 and 25	1922	Muhsam							Not stated
26	1922	A. Rosenstein	22	F	? 2	? German	Yes	Yes; hemeralopia since aet. 6 yrs.; optic atrophy; astigmatism, nystagmus, myopia	Not stated
27	1923	G. E. de Schweinitz		F	Not stated		Yes	Yes; visual defect at aet. 5 yrs.	Yes
28	1923	G. E. de Schweinitz		F	Not stated		Yes	Yes	Yes
29	1923	G. E. de Schweinitz		M	Not stated		Yes	Yes; visual defects in first months of life	Yes
30	1924	A. Frigerio						Blindness	Not stated
31	1924	Densler	12½	M	5		Yes; since infancy	Yes; visionary disturbance noticed on entering school; nystagmus	12 toes

LAURENCE-BIEDL SYNDROME—*Cont.*

Genital Dystrophy	Mental Deficiency	Sella Turcica	Basal Metab. Rate	Therapy	Result	Miscellaneous Notes	Characteristic Complete Syndrome	Partial Syndrome	Doubtful Cases
	? Yes	Diminished in size						Yes	
							? Yes		
Yes; no menses until 21 yrs.	Yes	Small with a plump sheer dorsum; brachycephaly		Pituitary, thyroid and ovarian ext.	Vision gradually improved and a gradual weight loss; menses reestablished		Yes		
Yes; no prostate	Yes	Normal, but with a sheer plump dorsum; brachycephaly		Same as Case No. 18	Improved	Short for age; 55 ins.	Yes		
Yes	Not definite but slow psychic and emotional responses	Sheer plump dorsum		Not stated		Mild oxycephaly; family history negative		Yes	
						Lues suspected but not proved. "Two other cases with same concentric diminution of visual fields." Boenheim believes Meisner's cases are a true Laurence-Biedl syndrome			Yes
						Author states that he saw two cases in same family with same disturbance as Meisner's patients. Possible consanguinity discussed			Yes
Yes; no menses until aet. 20	Yes			Not stated		Also had tuberculosis		Yes	
	No			Thyroid with ? pituitary ext.	Has maintained vision which was previously rapidly declining	Consanguinity, dwarfed in height and general symptoms of pituitary dysfunction			Yes
	Yes			Same as Case 27	Vision, mentality and general condition distinctly improved	Same as Case 27, but with mongolian facies		Yes	
	? No			Same as Case 27	No effect noted but it is doubtful if he continued the medication	Same as Case 27, except acromegalic features		Yes	
	Yes					Deafness familial			Yes
Yes	Yes	Wide and deep with a retroposed dorsum sellae pointed and short ante. clinoids; Tuberculum sellae eroded				Polydipsia; no polyuria	Yes		

TABLE OF REPORTED CASES OF

Case No.	Year	Author	Age	Sex	Children in Family	Race	Adiposity	Atypical Retinitis Pigmentosa	Polydactyly
32	1925	G. Deusch	30	F	6—One had 12 toes and a congenital heart	? German	Yes	Yes, but this did not appear until aet. 18 although fundi observed from aet. 5; congenital amblyopia, nystagmus, cortical cataract	No; syndactyly
33	1925	S. Solis-Cohen & E. Weiss	17	F	8—Sister to Cases 34, 35 and 36	Italian	Yes	Yes; visual defect appeared aet. 15, partial optic atrophy	Yes
34	1925	S. Solis-Cohen and E. Weiss	21	M	8—Brother of Cases 33, 35 and 36	Italian	Yes	Yes; visual defect at 16 yrs.; optic atrophy; contracted visual fields, myopia, astigmatism, nystagmus	Yes
35	1925	S. Solis-Cohen and E. Weiss	15	F	8—Sister of Cases 33, 34 and 36	Italian	Yes	Yes; visual defect at 13 yrs.; partial optic atrophy and contracted visual field	No
36	1925	S. Solis-Cohen and E. Weiss	11	M	8—Brother of Cases 33, 34 and 35	Italian	Yes	Yes; visual defect at 10 yrs.; no myopia or nystagmus	No
37	1925	D. McAlpine	15¾	M	6		Yes	Yes; visual defect since aet. 8	Yes 11 fingers 12 toes
38	1926	Zondek	14	M	? other normal boy	? German	Yes	Eyegrounds—nothing stated	No polydactyly
39	1926	Zondek	11	M	4—Three sisters normal	German	Yes since aet. 1	Yes; with definite choroid retinitis also; strabismus	No
40	1927	J. Bauer	7	F	One sister died; had polydactyly	German	Yes	Yes	Yes
41	1927	J. Bauer		M	Not stated	? German	Yes	Yes	Yes
42	1927	J. Ratner	24	F		? Russian Jew	Yes	Not found; coloboma of iris and choroid bilaterally	Not stated
43	1928	M. Ricaldoni and A. Isola	21	F	8—Sister to Cases 44, 45 and 46	? Uruguay	Yes	Yes; visual defect appeared early in life; nystagmus	11 toes
44	1928	M. Ricaldoni and A. Isola	12	F	8—Sister to Cases 43, 45 and 46	? Uruguay	Yes	Same as Case No. 43	11 fingers 11 toes
45	1928	M. Ricaldoni and A. Isola	19	M	8—Brother to Cases 43, 44 and 46	? Uruguay	Yes	Same as Case No. 43 with divergent left strabismus	11 fingers 11 toes
46	1928	M. Ricaldoni and A. Isola	16	M	8—Brother to Cases 43, 44 and 45	?Uruguay	Yes	Same as Case No. 43, but no strabismus	14 fingers 14 toes

LAURENCE-BIEDL SYNDROME—*Cont.*

Genital Dystrophy	Mental Deficiency	Sella Turcica	Basal Metab. Rate	Therapy	Result	Miscellaneous Notes	Characteristic Complete Syndrome	Partial Syndrome	Doubtful Cases
? No or only very mild	Yes	Enlarged; changes in dorsum sellae and ante. clinoids	Decreased	Thyroid ext. pituitary ext. intermittently on previous occasions	Loss 10 lbs.; no effects	All epiphyses ossified	Yes		
Yes: infantile uterus; no menses until aet. 17	Yes	Normal	—19%	Pituitary and thyroid ext.	No change in weight, mentality, or temperament. Girl said "saw better", but there was no objective confirmation of this	Ovarian cyst with torsion; short in height, 56½ ins.; glucose tolerance very poor	Yes		
Yes	Yes	Slightly small	—3%	Same as Case 33 for 8 mos.	No apparent effect	Short, 63 ins.; glucose tolerance poor; bone age probably normal	Yes		
Yes	Yes	Floor rather uneven; post. clinoids inclined backward	—29%	Same as Case 33	No apparent effect	Short, 54 ins.; bone age probably normal; glucose tolerance slightly poor		Yes	
Yes	Yes	Normal	—21%	Same as Case 33	No apparent effect	Height normal, 54 cm.; bone age probably normal; glucose tolerance normal		Yes	
Yes	? Yes	Normal		None		Negative Wassermann; no glycosuria	Yes		
Yes	Yes; idiocy			None		Hearing normal, dwarfed; Boenheim includes his case as a true Biedl syndrome; Zondek calls his case cerebral obesity			Yes
Yes	Yes. ? Imbecility	Normal	? High	None		Wassermann's negative in blood and spinal fluid		Yes	
Yes	Yes			None		Autopsy performed on one of cases; nothing pathological found	Yes		
Yes	? Yes			None			Yes		
		Steep, high dorsum sella				Author claims this condition equivalent to Biedl syndrome			Yes
Yes; menses appeared at 19 yrs.	Yes	Small, with elongated ante. clinoids, partially roofing sella		None		Consanguinous marriage. Marked dorsal scoliosis since aet. 12; all four had some retardation in epiphyseal age	Yes		
Yes	Yes	Small, with elongated ante. clinoids, partially roofing sella		None		Great irregularity in dental architecture; teeth small	Yes		
Yes	Yes	Small, with elongated ante. clinoids, partially roofing sella		None		?Congenital heart; marked genu valgum	Yes		
Yes	Yes	Small, with elongated ante. clinoids, partially roofing sella		None		Same as Case 45	Yes		

TABLE OF REPORTED CASES OF

Case No.	Year	Author	Age	Sex	Children in Family	Race	Adiposity	Atypical Retinitis Pigmentosa	Polydactyly
47	1928	H. Bernhardt	16	M	2—Brother to Case 48	Polish Jew	Yes	Yes; visual impairment aet. 4;nystagmus, astigmatism, myopia, divergent strabismus	2 extra rudimentary fingers
48	1928	M. Bernhardt	12	M	2—Brother to Case 47	Polish Jew	Yes	Optic atrophy but without pigmentary infiltration; nystagmus, strabismus, myopia;visual deficiency at aet. 1½ yrs.	12 fingers 13 toes
49	1929	M. Sterling	7	M	Not stated	? French	Yes	Yes; visual deficiency aet. 5; nystagmus	No; syndactyly
50	1929	H. Rieger and R. Trauner	6	F	6—One sister had polydactyly	? German		Yes; divergent strabismus, hypermetropia;astigmatism	Yes; 12 fingers
51	1929	M. J. Serejski	27	F	5	? Russian Jew		Yes; hemeralopia aet. 6; optic atrophy	11 fingers 11 toes
52	1929	H. Lisser	8	F	7—One brother died aet. 18 mos., had 12 toes	Spanish	Yes	Yes; strabismus	12 toes
53	1929	H. Beck	11	M	4—Brother of Case 54	Italian	Yes	Yes; optic atrophy	11 fingers 11 toes; with syndactyly
54	1929	H. Beck	10	F	4—Sister of Case 53	Italian	Yes	Yes; with left strabismus and optic atrophy	11 fingers
55	1929	W. Lange	15	M	8—One sister had polydactyly and mental deficiency	German	Yes; aet. 1½ yrs.	Yes; nystagmus	12 toes
56	1929	W. Lange	18	M	13	German	Yes	Yes	No
57	1929	W. Lange	12⅔	M	6	German	Yes	Yes	Syndactyly
58	1929	E. Boenheim	12	M	2	German-Italian	Yes	Yes	12 fingers 12 toes
59	1929	E. Boenheim	19	M	Not stated	Jewish	Yes	Yes	Yes
60	1929	E. Boenheim	28	M	3—Brother Case 61; one other brother had hemeralopia	? German	Slight	Yes	No

LAURENCE-BIEDL SYNDROME—*Cont.*

Genital Dystrophy	Mental Deficiency	Sella Turcica	Basal Metab. Rate	Therapy	Result	Miscellaneous Notes	Characteristic Complete Syndrome	Partial Syndrome	Doubtful Cases
Yes	? No	Large base somewhat flat	Normal	Thyroid ante. pituitary and calcium	Vision improved, weight reduced; metabolism increased, muscular tones better	Difficult forcepts delivery with frequent paralytic attacks, but consciousness intact; Wassermann negative; polydipsia	Yes		
Yes	? No	Large	Normal	Thyroid, ante. pituitary and calcium	Weight reduced, metabolism increased, musculature better, more active	Difficult forcepts delivery with frequent paralytic attacks but consciousness intact; Wassermann negative; polydipsia	Yes		
Yes	Yes			Not stated			? Yes		
? No	? No	Normal		Thyroid ext. for 18 mos.	No effects	Brachycephaly	? Yes		
None	Yes; I. Q. 22%	Entrance to sella narrow, base flattened; ? partially roofed in		None		Difficult forceps birth thought to be causative. Wassermann negative; oxycephaly; high grade left kyphoscoliosis	Yes		
	Idiot	Normal		None		Mental retardation and strabismus aet. 1; after 7 days of fever and stupor diagnosed ? pneumonia; bone age, 7–9 yrs.; blood calcium 10.4 mgm.; glucose tolerance decreased	Yes		
Yes	Yes	Large and irregular outline with high dorsum		Thyroid and whole pituitary ext. 4 mos.	Vision improved; loss of 18 lbs.; mentality definitely improved and continued thus for 1 yr.	? Normal bone age; very good hearing	Yes		
Yes	Yes	Increased in depth and somewhat shut in; large sinuses		Same as above	Same as above; loss of 17 lbs.	Same as above	Yes		
Yes	Yes	Normal		Iodides "Casbis"	None	Slightly tall for age	Yes		
Yes	Yes	Normal		None		Short for age, 60 in.; ? luetic tibial scars; Wassermann positive 1923 but negative without therapy in 1929		Yes	
Yes	Yes	Normal		Thyroid, pituitary, testicular and adrenal ext.	None	Wassermann negative	? Yes		
Yes	? Yes	Enlarged uniformly; ant. clinoids eroded	—21%	None		Feminine mammae; partial acromegaly	Yes		
Yes	? Yes						Yes		
Yes; libido diminished; impotent; female pubic hair		Normal	+27%	Whole and ant. pituitary per rectum	Vision definitely better; impotence disappeared	Impaired hearing		Yes	

TABLE OF REPORTED CASES OF

Case No.	Year	Author	Age	Sex	Children in Family	Race	Adiposity	Atypical Retinitis Pigmentosa	Polydactyly
61	1929	E. Boenheim	30	M	3—Brother Case 60; one other brother had hemeralopia	? German	No; slender	Yes	No
62	1931	J. McKinney		F	2—One brother died aet. 8, had 11 toes		Yes	Yes; myopia and nystagmus	12 toes 11 fingers
63	1931	G. M. Griffiths	5	F	6—One sister had syndactyly; one brother had 11 fingers and 11 toes		Yes	Yes; unilateral; strabismus, nystagmus and contraction of fields	12 toes with syndactyly, incurving little fingers, each having a small fleshy mass
64	1931	T. McCrae and E. Weiss	15	F	2	Polish-American	Yes	Yes; visual defect aet. 4; strabismus, nystagmus	12 toes
65	1931	H. Turner	13	M	4	American	Yes	No; fundi normal	12 fingers 12 toes, with syndactyly
66	1931	J. Orgaz	12	M	11—Two brothers had polydactyly	Argentinian	Yes	Yes; visual deficiency at 7 yrs.	11 fingers and 12 toes
67	1931	R. Bing (quoted from J. A. M. A. 98, 440, 1932)	17	M	6—Four are normal brother of Case No. 68	? Norwegian	? Yes	? Yes	? Yes
68	1931	R. Bing (quoted from J. A. M. A. 98, 440, 1932)	14	F	6—Four are normal sister of Case No. 67	? Norwegian	? Yes	? Yes	? Yes
69	1932	A. M. Ornsteen	12	M	6—Brother of patients No. 70 and No. 71	American	Yes	Yes; visual deficiency at 5 yrs.	No
70	1932	A. M. Ornsteen	2½	F	6	American	Yes	Yes; visual deficiency from birth	No
71	1932	A. M. Ornsteen	1½	F	6	American	Yes	Yes; visual deficiency from birth	No
72	1932	W. A. Reilly and H. Lisser	13	F	6—Sister of Case 73	Italian	Yes	? Yes; strabismus nystagmus, myopia; detached retinae with old vitreous hemorrhages; hemeralopia aet. 6	No

LAURENCE-BIEDL SYNDROME—*Cont.*

Genital Dystrophy	Mental Deficiency	Sella Turcica	Basal Metab. Rate	Therapy	Result	Miscellaneous Notes	Characteristic Complete Syndrome	Partial Syndrome	Doubtful Cases
Yes	Yes	Areas of calcification within sella	Normal	Whole and ant. pituitary per rectum		Impaired hearing; libido almost absent			Yes
	Yes; I. Q. 36% Oct., 1929, and 42% Feb., 1931	Slightly small		Thyroid and pituitary ext. for 15 mos.	No visual improvement; increased weight 100 to 116 lbs.; growth 2¼ ins.	Short for age; has nodding head spasms and choreiform movements; ?polydipsia and ? polyuria	? Yes		
	Yes	Small; high thick dorsum		Thyroid whole pituitary for 6 mos.	No effect; weight remained stationary	Tall for age, 43 ins.; bone age 7–8 yrs.; increased glucose tolerance; calcium 13 mgm. %; Wassermann negative. Positive thermic reaction of Cushing	? Yes		
Yes	Yes; I. Q. 35%	Normal	—15% to —12%	Whole pituitary grs. ii for 2 weeks then only thyroid ext. grs. v daily	30 lbs. loss in 20 mos.; mental improvement	Syndrome dated from illness at 4 yrs. with fever, somnolence, and head retraction for 2 weeks; mental deficiency since polyuria and polydipsia; spinal fluid, sugar tolerance, bone age normal; blood Wassermann negative	Yes		
Yes	Yes; I. Q. 50%	Very shallow with no evidence of clinoid processes		Liq. Pit. 40 drops and ant. pit. 1 cc. and thyroid ext. 25 grs. daily for 1 yr.; 1400 cal. diet	Lost 50 lbs. in 5 mos.; I. Q. rose to 76 at end of 1 yr.	Marked genu valgum and bilateral dislocation of patellae; oxycephaly; Wassermann negative; bone age normal; glucose tolerance increased		Yes	
Yes	Yes	Normal	45% minus	None		Consanguinity. Luetic father; Pt. had negative Wassermann; normal bone age	Yes		
? Yes	Yes		Low	Calcium, thyroid and pituitary extracts	No effect on vision; loss of weight; improved mentality		? Yes		
? Yes	Yes		Low	Calcium, thyroid and pituitary extracts	No effect on vision; loss of weight; improved mentality		? Yes		
Yes	Yes	Normal	Normal	None		Blood, urine and sugar tolerance normal; Wasserman negative		Yes	
Too young to determine	Yes; poor	Normal				Familial obesity, normal bone age, no consanguinity; patient died of pneumonia, no autopsy		Yes	
Too young to determine	Yes	Normal				Normal bone age		Yes	
? No	Yes; I. Q. 44%	Slightly enlarged	—21%	Thyroid grs. iii to v; whole pituitary gr. xv daily for 8 mos.	Vision distinctly improved objectively; loss of 40 lbs.; mentally brighter	Marked osteochondritis of dorsal vertebrae; no consanguinity; blood and spinal fluid serology, cytology negative		? Yes	

TABLE OF REPORTED CASES OF

Case No.	Year	Author	Age	Sex	Children in Family	Race	Adiposity	Atypical Retinitis Pigmentosa	Polydactyly
73	1932	W. A. Reilly and H. Lisser	11	F	6	Italian	Yes	Yes; hemeralopia since infancy, nystagmus, strabismus, myopia	No
74	1932	W. A. Reilly and H. Lisser	11	F	Unknown	American	Yes	? Yes; with some pigmentary clumping; choroid retinitis strabismus, nystagmus, congenitally blind	No
75	1932	W. A. Reilly and H. Lisser	19	F	7—All well	American	Yes	? Yes; with some pigmentary clumping; visual deficiency since aet 12 after ? sinus infection	No
76	1932	E. Weiss	16	F	4—A paternal relative had 6 fingers; sister of next patient	? American	Yes	Normal	No
77	1932	E. Weiss	26	F	4—A paternal relative had 6 fingers; also deaf; sister of patient No. 76	? American	Yes	Normal	No

Fourteen were Germans, 1 was German-Italian, 4 were English, 11 were Italian, 3 were Spanish, 5 were Jewish, 1 was Austrian, 1 Argentinian, 3 were French, 4 from Uruguay, 2 Norwegians, 6 Americans and in 24 instances the nationality was not mentioned.

Seventy-two were obese, 1 not so and 3 unstated as to obesity.

Sixty-one had atypical retinitis pigmentosa, 9 did not and in 7 it was not stated.

Forty-two had polydactyly, 26 did not and it was not stated in 9.

Fifty-four had genital dystrophy, 7 did not and in 17 this was not stated.

Sixty had mental deficiency, 7 did not and in 11 it was not stated.

The sella turcica was small in 11, large in 7, normal in 12 and of Biedl type (large plump, sheer dorsum sellae) in 7; in 28 no comments were made on the sella turcica.

Basal metabolic rate was reported in 18, high in 3, low in 11, and normal in 4.

Of 7 glucose tolerance tests 3 disclosed an increased tolerance, in 2 it was decreased and in 2 normal.

Nuclear osteogenesis was normal in 10, accelerated in 4 and retarded in 4.

Wassermann (blood) was negative in 17 and when positive, it was questionably so (4 instances).

Prominent in miscellaneous notes were the following items:

Consanguinity occurred in three families; brain tumor was diagnosed in 3 cases, but never proven; impaired hearing occurred 5 times; polyuria and polydipsia 6 times; oxycephaly in 3 cases and microcephaly in 5.

LAURENCE-BIEDL SYNDROME—*Cont.*

Genital Dystrophy	Mental Deficiency	Sella Turcica	Basal Metab. Rate	Therapy	Result	Miscellaneous Notes	Characteristic Complete Syndrome	Partial Syndrome	Doubtful Cases
? No	I. Q. 36%		? Low	As above	Vision does not continue to fail; loss of 20 lbs.	As above except spinal fluid not examined		Yes	
? No	Yes			Pt. did not return to clinic		Mild microcephaly; incurved little fingers; bone age of 12 yrs; Wassermann negative			Yes
Yes, no menses until aet. 15 yrs.	No	No-mal		None		Short height, 56 ins.			Yes
Yes	Yes	Slightly small	24 plus %	Thyroid, pituitary and ovarian extract	No effect on hearing; no weight increase	Short, 55½ ins.; deaf			Yes
Yes	Yes								Yes

TREATMENT

From the singular and eccentric character of the elements involved in this syndrome it would at first thought seem quixotic to expect much from any form of therapy—especially any directed toward vision.

Perusal of the therapy column in Table 1 shows that many considered the condition so hopeless that no therapy was attempted, or failed to mention whether any treatment was administered.

Seven authors (Schweitzer, Bertoletti, Von Jaksch, Lange, Rieger and Traumer, Solis-Cohen in three of four cases, and de Schweinitz in one of three cases) failed to note any improvement. Opotherapy, principally thyroid and pituitary, and occasionally sometimes with the addition of gonadal extracts, was the choice of these clinicians.

However, many authors have noted improvement on thyroid with pituitary and ovarian extract used singly or in various combinations. Of the complaints obesity was reduced not infrequently; (De Cyon, 27 lbs. in 4 months; Reilly and Lisser, 40 lbs. in one patient and 25 lbs. in another, during 8 months; Turner, 50 lbs. in 1 year; McCrae and Weiss, 30 lbs. in 20 months; Beck, 18 lbs. in 4 months; Deusch, 10 lbs.). The next complaint most frequently improved by glandular treatment was the mental retardation. (de Schweinitz, 1 case; Beck's 2 cases; McCrae and Weiss, 1 case; Turner—where the intelligence rose from 50 to 76 per cent in 1 year; Reilly and Lisser, 2 cases; Bing, 2 cases.) Coincident with the mental improvement there occurred increased animation, livelier conduct and better muscle tone, probably attributable to the administration of thyroid substance.

Beneficial effects on poor vision were less frequently reported. De Schweinitz mentions one case where vision remained stationary, whereas previously it had been decreasing. Vision was improved in the following: de Schweinitz, 1; Biedl, 2 patients; Solis-Cohen, 1 questionable; Bernhardt, 1; Beck, 2, better for 1 year; Boenheim, 1. In our report the beneficial results can hardly be questioned though our previous viewpoint was nihilistic. E. C., Case 1, for nearly four years had had no vision except for light and to a very slight degree for form; and needed the constant attendance of her mother. Now, after 8 months, she is able to see her way about, cares for herself and can play, and much to our surprise, can read her younger sister's books of larger print. While her mentality precludes definite measurement, there is no doubt of her visual improvement.

SUMMARY

1. A careful search and appraisal of the literature has revealed 73 cases which were entitled in the writers' opinion to the diagnosis of Laurence-Moon-Biedl Syndrome. These have been analyzed in tabular form. The authors have added four more cases, two unquestionable instances of the complete syndrome and two examples where the syndrome was only partially manifested, making 77 cases in all.

2. Two of our patients responded surprisingly well to endocrine therapy. Not only weight loss and increased animation occurred but also definite improvement in vision.

REFERENCES

Bardet, G.: Univ. Paris Thesis, **470**: 107. 1920.
Bauer, J.: Innere Sekretion. 1927. Springer, Berlin u. Wien.
Beck, H.: Endocrinology, **13**: 533. 1929.
Bernhardt, H.: Ztschr. f. klin. Med. **107**: 488. 1928.
Bertolotti, M.: Gior. d. r. Accad. di med. di Torino, **20**: 6. 1914.
Biedl, A. and W. Raab: Deutsche med. Wchnschr. **48**: 1630. 1922. Wien Arch. f. inn. Med. **7**: 443. 1924.
Bing, R.: Norsk mag. f. laegevidensk, **92**: 933. 1931. Abstracted J. A. M. A. **98**: 440. 1932.
Boenheim, F.: Endokrinologie, **4**: 263. 1929.
Borchardt: Inkretologie. 1927. Bayer u. van den Velden, Leipzig, or Klin Konstitutionlehre. 1924. Berlin u. Wien.
Chaillous: Ann. d'ocul. **158**: 100. 1921.
DeCyon: Bull. Acad. de Méd., Paris, **40**: 444. 1928.
Denzler, E.: Jahrb. f. Kinderh. **107**: 35. 1925.
DeSchweinitz, G.: Tr. Ophth. Soc. U. Kingdom, **43**: 12. 1923.
Deusch, G.: Deutsche Ztschr. f. Nervenh. **107**: 35. 1924.
Frigerio, A.: Zentralbl. f. d. ges. Ophth. S634. **14**: 635. 1925.
Griffiths, E.: J. Neurol. & Psychopath. **12**: 53. 1931.
Grossman: Wien. med. Wchnschr. **58**: 742. 1908.
Hansen, S.: Hospitalstid. **63**: 417. 1920.
Hutchinson, J.: Arch. Surg. (Hutchinson's) **11**: 118. 1900.
Kruckman u. Meyer: Duetsche med. Wchnschr. **34**: 574. 1908.
Lange, W.: Allg. Ztschr. f. Psychiat. **86**: 404. 1927.
Laurence, J. Z. and R. C. Moon: Ophth. Rev. **2**: 32. 1866.
Lisser, H.: Endocrinology, **13**: 533. 1929.
Madigan, J. J. and J. V. Moore: J. A. M. A. **70**: 669. 1918.
McAlpine, D.: Rev. neurol. **37**: 661. 1930.
McCrae, I. and E. Weiss: M. Clin. North America, **14**: 825. 1931.
McKinney, J. M.: J. Nerv. & Ment. Dis. **74**: 50. 1931.
Meissner: Klin. Wchnschr. **1**: 497. 1922.

Muhsam: ibid.
Ornsteen, A.: Am. J. M. Sc. **183:** 256. 1932.
Orgaz, J.: Rev. Med. latino-am. **16:** 966. 1931.
Ratner, J.: Monatschr. f. Psychiat. u. Neurol. **64:** 283. 1927.
Ricaldoni, M. and A. Isola: Bull. et mém. Soc. méd. d. hôp. de Paris. **52:** 1131. 1928.
Rieger and Trauner: Ztschr. f. Augenh. **68:** 235. 1927.
Rosenstein: Klin. Monatsbl. f. Augenh. **68:** 204. 1922.
Rozabel-Farnes: Rev. clin. de Madrid. **9:** 401. 1913.
Schweitzer, F.: Soc. Argentina de Pediatria, Sept. 22, 1917.
Serejski, M. J.: Med. Klin. **25:** 1620. 1929.
Solis-Cohen, S. and E. Weiss: Am. J. M. Sc. **169:** 489. 1925.
Turner, H.: J. Oklahoma M. A. **24:** 148. 1931.
Variot and Bouquier: Gaz. d. hôp. **93:** 613. 1920.
Von Jaksch, R.: Med. Klin. **8:** 1931. 1912.
Weiss, E.: Am. J. M. Sc. **183:** 268. 1932.
Zondek, H.: Die Krankheiten der Endokrinen Drusen, Berlin, 1926.

A CASE OF PARATHYROID DEFICIENCY

GEORGE H. HOXIE
KANSAS CITY, MO.

In his article on Diseases of the Parathyroid Gland in the George Blumer edition of the Billings-Forchheimer Therapeusis of Internal Diseases, William N. Berkeley has this to say on the subject of clinical forms of parathyroid disease: "In medical literature for the past twenty years the parathyroids have been peculiarly the victims, so to speak, of unscientific observation. The 'office scientist,' the careless and superficial reviewer of literature, the laboratory man who never studied that chapter in logic which treats of fallacies, have done great harm. A mixed multitude of metabolic and convulsive disorders have been laid at the door of the parathyroids, and been successfully treated by a miscellaneous assortment of untested and unstandardized commercial and home-made preparations of the same gland."

Further on he says: "In America hardly 100 adult cases have been reported (of idiopathic tetany); in small children it is more common. On the continent of Europe it occurs frequently at all ages. Friedrich Kraus used to show many cases in Vienna in former years. . . .McCarrison describes it as an endemic disease in the Himalayas, especially among childbearing women, and almost exclusively in the spring months. Special clinical types are described as incident upon gastric dilatation, upon pregnancy, and in children upon rickets. Von Frankl-Hochwart connects it also with acute infectious diseases, and with certain cases of chronic poisoning."

Our usual conception of tetany is based upon the definition of Frankl-Hochwart, who considered it a tonic intermittent bilateral or painful cramp, which, without loss of consciousness, involves the muscles of the arms and hands particularly, which latter are held wedge-shaped or in the obstetric position. That is, we have thought it a tonic rather than clonic seizure. If we can disabuse our minds of the conviction that lowered calcium metabolism leads only to tonic spasms, and admit that such a calcium deficiency may manifest itself in excessive nervous irritability or unstable equilibrium, we can appreciate the reports of Timme and will look for this condition in many of the puzzling syndromes confronting us in daily practice.

In spite of Berkeley's strictures on the subject, I should like to report a case of clonic spasm which was relieved by the administration of calcium and parathormone.

CASE HISTORY

Mrs. J. A. W. of Lexington, Missouri, a patient of Dr. C. T. Ryland's, was seen first November 2, 1929, when she was 38 years old. The description of her subjective symptoms was poorly given at first. She said she was subject to

nervous spells, that she cried, that the muscles jerked, that she had had four such nervous spells in the preceding week. The first one had occurred following a sore throat and chill in June. It developed that by nervous spells and jerking she meant a clonic spasm of the lower extremities, sometimes extending up into the arms. These attacks would come on when she attempted to stand, when she attempted to talk, or to put forth any effort. She had backache, legache, palpitation, abdominal symptoms—sometimes in the nature of indigestion, sometimes in the nature of colic.

Past history: She had had the usual children's diseases. The most important of these had been diphtheria at 8 years. One would infer from her story that she had never been quite strong since that time. She had had a tonsillectomy at 14, and had had relatively few colds and sore throats.

The *present trouble* probably began five or six years before, but her first real attack was 4 years before when her last child was born. She was then in bed two months. The trouble recurred again the next year when she was in bed for three weeks.

Menstruation began at 14 years of age. The periods were irregular, tending to come sooner than four weeks. The flow was scanty and lasted only one or two days. There were no cramps. Of late years she became weak and lifeless all over for about a week or ten days before and after the menses. During our period of observation we noticed that no menstrual flow appeared unless she sat up in bed, or stood on her feet.

Her appetite was irregular. Between the menstrual periods it became fairly good. The bowels did not act at all except with an enema.

The reflexes were all exaggerated, but the Trousseau and Chvostek signs were negative.

She had frequent attacks of palpitation and her blood pressure varied between wide limits. The first day it was 130/90, but at other times it dropped as low as 80/60.

The temperature ranged within normal limits.

The blood count, at the beginning, showed hemoglobin, 90 per cent; red cells, 4,360,000; white cells, 6,500; polymorphonuclear leucocytes, 60 per cent; large lymphocytes, 2 per cent; small lymphocytes 37 per cent; transitional cells, 1 per cent. Blood analysis at that time gave: non-protein nitrogen, 34.1; creatinin, 1.5; sugar, 95; and the chlorides, 560. It was not until several months later that it was decided that in spite of the negative Trousseau and Chvostek signs the calcium might be deficient. The calcium was then studied. Then it was shown to be 9.5. When calcium therapy was instituted and parathormone given an immediate convalescence began. That this was not due to the cessation of the menses was shown by stopping the parathormone for several months when the patient dropped back to her former condition of nervousness. Cod liver oil did not appreciably change the picture. It had to be given in the form of an emulsion—Schlotterbeck's Mistura Glyconin Composita.

Mrs. W. could not stand upright on the scales to be weighed. In fact, whenever she attempted to do anything or make any muscular effort, the tremor appeared, and prevented consecutive muscular action. Consequently attempts to secure an accurate evaluation of the basal metabolism gave merely approximations. Such attempts were made on three different occasions. The results were within normal limits, i.e., between a plus 4 and a minus 11.

Her greatest weight had been 176 pounds, it dropped as low as 127 pounds, and November 13, 1931, when she was seen here for the last time, it was 139 pounds.

The patient was seen by several other physicians, but no one could identify the type of muscle jerking and spasm with anything with which they had had previous experience.

She was kept in a nursing home (in bed) for several months.

The various endocrine products were used including ovarian, pituitary and adrenal, without more than temporary benefit. Psychotherapy helped to the extent of securing her cooperation.

The curve of disability seemed to be subject to the menses which brought her down from whatever improvement she had achieved in the interval, back to complete prostration—and spasms whenever one disturbed her, or she attempted to put forth any effort. Finally at her suggestion the physicians agreed to produce an artificial menopause. Radium needles were used, but instead of a cessation of the menses, an increased flow resulted, then some irregularity. During this interval the calcium parathyroid therapy was instituted and the patient began to mend. She was able to get up and take short walks. Then she went home,

still continuing the parathormone and a calcium rich diet. She stopped her parathormone and a relapse resulted. The menopause was completed with two exposures to the x-ray—but even then she had to have parathormone occasionally.

COMMENT

Falta's description of hypoparathyreosis—or tetany—furnishes the nearest approach to the description of the symptoms found in this case. The only objection to calling it a case of tetany would lie in the clonic nature of the symptoms as opposed to the ordinary tonic or spastic contracture type. This patient had the intention spasms of Frankl-Hochwart. She showed the susceptibility to adrenalin. The increased sweating was present. The lability of the heart action was manifest. The pallor of the face was pronounced. The digestive disturbances were as described by Falta. According to Falta's description it may be spoken of as a case of tetany due to the exhaustion produced by the repeated pregnancies and childbirth. But it should be emphasized here again that the stopping of the menstruation of itself did not stop the tendency to the clonic spasm. This essential condition of the disease was not relieved until parathyroid was given and continued.

SUMMARY

The case is reported of a woman suffering chronically from clonic spasms. The Trousseau and Chevstek signs were negative. The menstruation was depressed but caused an aggravation of the spasms. The blood calcium level was 9.5. Under parathormone and high calcium diet the symptoms were relieved. It is concluded that clonic as well as tonic spasms may result from parathyroid deficiency.

THE ESTIMATION OF ESTRIN AND THE FOLLICLE-STIMULATING HORMONE IN THE URINE AS AN INDEX OF THERAPY IN MENSTRUAL DYSFUNCTION*

RAPHAEL KURZROK, Ph.D., M.D.
With the assistance of James Boylan, M.D., Stanley Goldman, B.S., and Margaret A. Creelman, A.B.

(From the Departments of Obstetrics and Gynecology, and Biological Chemistry, and Sloane Hospital, College of Physicians and Surgeons, Columbia University.)

NEW YORK

In order to find some rational basis for the treatment of various menstrual disorders, we have studied, in a group of 300 cases, the occurrence in the urine of estrin and of the follicle stimulating hormone from the anterior pituitary gland (APH-A). Zondek (8) has shown that APH-A is not found in the urine of normally menstruating women, but is found on cessation of ovarian function due to castration, x-ray sterilization, menopause, or in certain amenorrheas, during pregnancy and in cases of genital carcinoma. Various observers found estrin in the urine of women during their functional sex life. By means of a method described by Kurzrok and Ratner (4) it was shown that a woman during her active sex life, except during pregnancy, excretes in her urine ten to twenty, rarely thirty, rat units of estrin per liter of urine. This excretion varies a little during the menstrual cycle. The excretion of less than ten rat units per liter may be considered as estrin hypofunction, and the excretion of more than 30 rat units per liter as estrin hyperfunction.

The method that we employ is as follows. A twenty-four-hour specimen of urine is collected beginning with a first morning specimen. The urine during collection is kept in a cool place and no preservative is added. The following morning the first specimen is collected separately and utilized for the APH-A determination. This is done by the method of Zondek (8). A portion of the twenty-four-hour specimen, 750 cc. is utilized for the estrin determination.

On the basis of the presence or absence of estrin and APH-A the cases may be divided into four types, with one group subdivided by the quantitative results of the estrin test, as indicated in the classification below. The clinical conditions represented by each group are also shown.

Type I. Estrin—present; APH-A—absent.

(A) Estrin 10-20 rat units per liter=normal function.

(B) Estrin <10 rat units per liter=hypofunction with oligomenorrhea or hypomenorrhea, occasionally amenorrhea.

*This research was aided by a fund from The Chemical Foundation.

(C) Estrin > 20 rat units per liter=polyhormonal amenorrhea of Zondek, polymenorrhea and hypermenorrhea, cystic and glandular hyperplasia of the endometrium.

Type II. Estrin—absent; APH-A—absent. Distinct hypofunction with amenorrhea, hypomenorrhea or oligomenorrhea.

Type III. Estrin—absent; APH-A—present. Cessation of ovarian function—castration, radiation, spontaneous menopause, menopause precox.

Type IV. Estrin—present; APH-A—present. Pregnancy. Genital carcinoma in women of child-bearing age. Glandular syndromes—thyroid, pituitary.

The presence of estrin in the urine implies a functioning anterior pituitary gland, for without the anterior pituitary there is no ovarian function. Apparently whatever APH-A is produced is taken up by ovaries for their proper functioning. When the follicular apparatus of the ovary ceases to function, then APH-A is no longer utilized and it is excreted in the urine. Estrin has an inhibiting influence* upon APH-A production, according to Moore and Price (6), therefore when the production of estrin ceases, there is an increase in APH-A and this additional quantity is excreted in the urine. Hence, "Estrin—positive; APH-A—negative" speaks for a normally functioning anterior-pituitary ovarian chain, in so far as the follicular apparatus is concerned. Estrin is only one of the hormones required in normal sex function, for menstruation requires the co-ordination of many hormones. Estrin controls the proliferative phase of the menstrual cycle. The phase of secretion is under control of progestin, and finally the actual hemorrhage is possibly the result of a separate hormone having its origin in the anterior pituitary. The production of both estrin and progestin is controlled respectively by the two gonad stimulating hormones, APH-A (follicle stimulating hormone) and APH-B (luteinizing hormone). Anterior pituitary hormones A and B do not act simultaneously, but B follows A, its action being inhibited by ovulation which in turn is probably controlled by another hormone. The hormones of the thyroid and adrenal probably play some part, at present undetermined, in this reaction. No single hormone can replace another hormone in this co-ordinated system, and the administration of estrin in every dysfunction appears irrational. Estrin should be used only when it is absent or deficient. We feel that its concentration in the urine reflects its concentration in the blood stream. The advisability of giving estrin depends upon its absence or presence in the urine.

The various groups of our table are utilized as an index of therapy in the following manner: If the result of the urine examination is Estrin—positive, 10-20 rat units per liter; APH-A—negative, we feel that we are dealing with a normally functioning system of sex hormones. Normally

*For a very excellent and comprehensive review of the interrelationship between the anterior hypophysis and the ovaries the reader is referred to two articles by C. F. Fluhmann in Am. J. Obst. & Gynec., **18**: 738, 1929, and **22**: 803, 1931.

menstruating women who do not at the same time present some endocrinal syndrome are of Type I. If, nevertheless, such a patient presents an amenorrhea we feel that the cause of the amenorrhea is neither a deficiency in estrin nor in APH-A. Some other hormone is at fault. Failure to yield therapeutic relief has always resulted from the administration of either of these hormones,* and their use in this type of amenorrhea has definitely been abandoned. The other hormones that might be involved are not available for clinical use and for this reason this form of amenorrhea has given us the poorest clinical results.

As a subgroup in Type I there is a group in which estrin is found in amounts less than 10 rat units per liter of urine. Clinically the picture is either one of amenorrhea, hypomenorrhea or oligomenorrhea. The hypofunction may be either on the part of the anterior pituitary or the ovary. In some cases we give both prolan (200-400 units per week) and estrin (50-100 units per week). In more cases prolan alone is now given. When estrin alone is given in large doses over a period of months to young patients who have hypomenorrhea or oligomenorrhea these patients may stop menstruating completely. This surprising mishap occurred early in our series in several cases where a distinct genital hypoplasia was present. The reason for this is probably indicated by the work of Leonard, Meyer and Hisaw (5), who found that the injection of follicular hormone prevents the ovaries of immature rats from reaching full growth and development as indicated by the weight of the glands. This decrease in weight is the result of a diminished number of follicles reaching maturity and a subsequent smaller number of corpora lutei. Patients with genital hypoplasia are in a sense immature or maturing organisms. Estrin in this group should be used with great caution.

In speaking of this group (genital hypoplasia) it is worth noting that many excrete 10-20 rat units of estrin per liter of urine. Our best results in this group, and they were not frequent, were obtained in patients under 25 years of age, by use of large doses of prolan alone. It is quite possible that not only APH-A but also the general body growth hormone may be necessary to stimulate the growth of these small uteri. Younger people who probably have this growth hormone would most likely benefit from prolan, as our results would seem to indicate. Evans and his co-workers (2) found that gonadal stimulation in hypophysectomized animals may be obtained with prolan when it is given along with an extract of the anterior pituitary growth hormone.

A third subgroup of Type I is formed by patients who excreted more than 20 rat units per liter of urine. A number of patients have exceeded 60 rat units per liter. Clinically we frequently find hypermenorrhea or polymenorrhea. The endometrium usually shows cystic and glandular hypoplasia. This pathological condition in which the endometrium presents an exaggerated proliferative phase of the menstrual cycle is caused

*We are greatly indebted to the Winthrop Chemical Co., Inc., for a generous supply of Prolan.

by an excessive production of estrin. It has recently been discussed from this angle by Fluhmann (3) as well as by Burch, Williams and Cunningham (1). It is evident that the administration of more estrin will merely increase the bleeding. The inhibition of the APH-A-estrin system is indicated. APH-B has recently been given by Novak and Hurd (7) with considerable success to a group of subjects showing this phenomenon. Progestin would have the same beneficial effect. We are now preparing it with this purpose in mind.

In addition to this group that bleeds excessively there is another group with the same high estrin excretion, but which clinically presents an amenorrhea, the so-called polyhormonal amenorrhea of Zondek (8). The uteri in these cases are somewhat enlarged and softened and give the impression of a very early pregnancy. Here again the administration of either APH-A or estrin is contra-indicated.

In Type II the APH-A test is negative and the estrin test is negative. This represents a distinct hypofunction of the APH-A-estrin system. Which of the two glands is primarly involved is unknown. Clinically the picture is usually amenorrhea, hypomenorrhea or oligomenorrhea. The few cases of this type that had relatively normal periods presented some endocrinal dysfunction. Although many cases of this type have responded well to large doses of Prolan (400 rat units per week) combined with small doses of estrin (50 to 100 rat units per week), cases of long standing amenorrhea have failed to give a response to the treatment. In some instances the treatment had to be maintained for several months before a period appeared. The next period usually appeared within two months. Many cases in this group completely failed to respond to treatment. The causes for the failures were not definitely known, but several factors may be considered. First, the potency of the prolan varied with the different batches. The ampules were labeled 100 rat units, but in the majority of instances the average was about 50 rat units. Secondly, there seems to be a renal threshold for prolan. When prolan is given in large doses, frequently repeated, it can be found in the urine in large quantities. Whether the threshold value varies in the same patient from time to time, or whether there is a variation between different patients, we do not know, Furthermore, the factors controlling this renal threshold are at present unknown. Again, is excretion by way of kidney the only way prolan is eliminated?

Type III (estrin—present; APH-A—absent) appears to be a more advanced stage of hypofunction than Type II. In Type III all ovarian function seems to have ceased. This picture was always encountered after operative castration and within a few months after complete x-ray sterilization. Some cases of the x-ray group show this combination as early as one or two months after the last x-ray treatment. Certain cases of spontaneous menopause also fall into this group. The excretion of APH-A is not always constant, there being irregular quantitative variations from

time to time. Apparently, in spontaneous menopause, the picture may change from estrin—absent, APH-A—present, to estrin—present, APH-A —absent, occasionally passing through a phase where both hormones are present simultaneously, and then back again. With each appearance of estrin in the urine there is an amelioration of the menopause symptoms. In all our cases of menopause the patients were treated on the basis of the result of the estrin test in the urine. Subjects that did not show estrin in the urine were given estrin in the form of Sistomensin, with very distinct therapeutic relief.

Type IV, estrin—present; APH-A—present is found in pregnancy, genital carcinoma in women of child-bearing age, and in certain endocrine dysfunctions. The latter group will be considered in a separate paper. Except for this group, cases classified as Type IV were not given hormonal medication.

SUMMARY

An attempt has been made to classify menstrual dysfunctions on the basis of the excretion of estrin and the follicle stimulating hormone (prolan A) in the urine. Three hundred cases were thus studied. Estrin was quantitatively estimated by the method of Kurzrok and Ratner and prolan A by the alcohol precipitation method of Zondek. The basis for this work was the fact that normally menstruating women did not excrete prolan A in the urine, but excreted estrin 10-20 R.U./L. Four types of excretion are possible when these hormones are considered together, and these types furnish an index of treatment.

Using the groupings as a guide the therapeutic results have been satisfactory.

REFERENCES

1. Burch, J. C., W. L. Williams and R. S. Cunningham: Surg., Gynec. & Obst. **53**: 338. 1931.
2. Evans, H. M., K. Meyers and M. E. Simpson: Proc. Soc. Exper. Biol. & Med. **28**: 845. 1931.
3. Fluhmann, C. F.: Surg. Gynec. & Obst. **52**: 1051. 1931.
4. Kurzrok, R. and S. Ratner: Am. J. Obst. & Gynec. 1932. (In press.)
5. Leonard, S. L., R. K. Meyers and F. L. Hisaw: Endocrinology, **15**: 17. 1931.
6. Moore, C. R. and Dorothy Price: Proc. Soc. Exper. Biol. & Med. **28**: 38. 1930.
7. Novak, E. and G. B. Hurd: Am. J. Obst. & Gynec. **22**: 501. 1931.
8. Zondek, B.: Die Hormone des Ovariums des Hypophysenvorderlappens: Untersuchungen zur Biologie und Klinik der weiblichen Genitalfunktion. Mit einem Anhang: Die hormonale Schwangerschaftsreaktion aus dem Hain bei Mensch und Tier. Pp. 251, 238, 240. Springer, Berlin, 1931.

FOLLICULAR HORMONE IN THE URINE AS AN INDEX OF THERAPY IN THE MENOPAUSE*

RAPHAEL KURZROK, Ph.D., M.D.

(From the Departments of Obstetrics and Gynecology, and Biological Chemistry, and Sloane Hospital, College of Physicians and Surgeons, Columbia University.)

NEW YORK

The treatment of menopausal symptoms has yielded varying results in the hands of different gynecologists. Some report good results and others poor results from organotherapy. The same observer often finds that among his own cases there are some patients who are greatly benefited by the administration of some form of ovarian hormone, while others are not benefited at all. We have found that those patients who are not benefited by ovarian therapy have ovarian hormone in the urine while those that are benefited have none.

By means of a method previously described we have determined that every normal woman during her active sex life excretes from 10 to 20 rat units of follicular (female sex or ovarian) hormone per liter of urine. This level of excretion is fairly constant, though there are minor variations within these limits during the menstrual cycle.

Cases of menopause may be divided as follows:

(1) No ovarian hormone found in urine.
   (a) Artificial menopause (by operation or x-ray).
   (b) Some cases of spontaneous menopause.

(2) Ovarian hormone present in the urine.
   (a) Some cases of spontaneous menopause.

The subjects that show no ovarian hormone in the urine are very distinctly benefited by therapeutic injection of the hormone, while those that show ovarian hormone in the urine are not at all benefited by the treatment. When both ovaries have been removed at operation or when sterilization due to radiation is complete, no follicular hormone is to be found in the urine. In the spontaneous menopause group the subjects that menstruate normally and have menopausal symptoms, ovarian hormone is always found in the urine, and the administration of more ovarian hormone is of no benefit; in fact, one often gets the impression that the patient is made worse. When the patient menstruates infrequently and the excretion of ovarian hormone is sporadic, then follicular hormone is beneficial. In subjects that are not menstruating, follicular hormone may

*This research was aided by a fund from The Chemical Foundation.

or may not be found in the urine; it is only in the latter group that good results are obtained.

All cases with menopausal symptoms are investigated and treated in the following way: A twenty-four-hour specimen of urine is collected, from 7 a.m. to 7 a.m. The urine collected at 7 a.m. at the end of the twenty-four hours is kept in a separate bottle. The larger quantity of urine collected on the previous day is subjected to a quantitative follicular hormone determination. The separate morning specimen is tested for the presence of the gonadal stimulating hormone, prolan A, by the method of Zondek (2). When ovarian function has ceased the findings are as follows: Ovarian hormone, negative; prolan A, positive. Zondek has shown that when the ovaries cease functioning (by castration or spontaneously) prolan A immediately appears in the urine. On the other hand, if the ovaries are functioning ovarian hormone is found in the urine and prolan A is absent. Only when there is no ovarian hormone in the urine do we feel that follicular hormone, as a therapeutic measure, is indicated. We can see no reason for injecting ovarian hormone when the patient is already excreting considerable quantities of the hormone in her urine.

We have found that small doses of follicular hormone, when administered as an oily solution intramuscularly, are adequate to control the menopausal symptoms. We give 2 cc. of sistomensin, 5 rat units per cc. once a week. No ovarian hormone is given by mouth. The occurrence of flushes, sweats, dizzy spells and palpitation is markedly reduced. The patients feel much better in general. The effect of a single treatment lasts from seven to ten days and then gradually wears off and the symptoms recur. The patients are quick to notice this change and are therefore very prompt in returning for treatment every week. We have utilized this form of treatment in more than one hundred patients, for periods ranging from 3 months to a year. How long we shall have to continue the treatment we do not as yet know.

We treat menopause patients that show ovarian hormone in the urine by means of triple bromides and calcium lactate, the purpose being to depress the irritability of the vasomotor and the other centers involved. The results are often fair and often unsatisfactory. Follicular hormone in this group is not at all effective. These observations would seem to show that follicular hormone is in some way related to the causation of the menopause symptoms, but that its presence or absence is not the only factor involved.

SUMMARY

Menopause cases may be divided into two groups: One group shows follicular hormone in the urine, and the other group does not. One hundred cases of menopause were thus studied. The hormone was determined by the method of Kurzrok and Ratner. Follicular hormone is of benefit only in that group in which no hormone is to be found in the urine. The

therapeutic results are very good when the cases are treated according to this grouping.

The author wishes to express his indebtedness to Dr. James P. Boylan and to Stanley Goldman and Margaret Creelman for their clinical and technical assistance in this work.

REFERENCES

1. Kurzrok, R. and S. Ratner: Am. J. Obst. & Gynec. 33. 1932. (April.)
2. Zondek, B.: Die Hormone des Ovariums und des Hypophysenvorderlappens: Untersuchungen zur Biologie und Klinik der weiblichen Genitalfunktion. Mit einem Anhang: Die hormonale Schwangerschaftsreaktion aus dem Hain bei Mensch und Tier. Pp. 244, 252. Springer, Berlin, 1931.

THYREOTOXICOSIS AND TETANY

SOME ASPECTS OF THE MINERAL METABOLISM IN MORBUS BASEDOWI*

E. ASK-UPMARK
From the Medical Clinic (Director: Professor Sven Ingvar) of the Royal University of Lund, Sweden

Tetany can be observed in Morbus Basedowi in two quite different conditions: on the one hand, as a postoperative complication, on the other hand, during the course of cases without operation. The former variety of tetany is not altogether uncommon, especially perhaps in America, where thyroidectomy as a rule is more radical than in certain European clinics, where subtotal resection is the usual method of operation. This kind of tetany is due to a parathyroid insufficiency dependent upon operative lesions. Hunter reports that Lahey, as a routine, examines the specimens removed at operation and, if any tissue suggesting parathyroid is found, he transplants it into the sternomastoid muscle, though reserving a portion for histological examination. The postoperative tetany is pathogenetically explained and need not be dealt with here.§ The tetany, on the contrary, appearing during the course of a thyreotoxicosis before operation is carried out, seems to offer a certain interest. On the one hand, there are only a few cases described and because of this it seems defensible to report also solitary cases observed. On the other hand, the pathogenesis of these cases is for the present quite obscure, on account of which an analysis appears to be desirable, especially with consideration of the investigations of the metabolic relations in hyperthyroidism that have been carried on during recent years. The present study is based partly upon a case of tetany in Morbus Basedowi, observed in the Medical Clinic of Lund, partly on certain recent pathophysiological studies of metabolic conditions in hyperthyroidism. This paper consists, first, of an attempt at an analysis of the pathogenetic relations of the tetany observed in cases of thyreotoxicosis, and, secondly, of a discussion of some further problems connected with Basedow's disease.

PROTOCOL

The case reported was observed in the clinic from the 10th to the 19th of November, 1930, on which day the patient was transferred to the surgical clinic for operation.

The subject was a married man aged 47, an Inspector of railroads.

History. Heredity was without importance. As a child he had pertussis and measles, otherwise he enjoyed good health up to 1918 when he acquired "the Spanish disease." After that he had very frequent colds. The presenting disease began about 20 months before admission in connection with pneumonia and after that progressed especially rapidly after a severe angina four months

*In the present paper the terms Morbus Basedowi, hyperthyroidism, hyperthyreosis, thyreotoxicosis and exophthalmic goiter are used as synonyms.

§The (theoretical) possibility, however, that the thymolymphatic system can to a certain degree be responsible for the postoperative tetany is mentioned below.

previous to admission. His troubles have consisted of general lassitude, nervousness and cardio-irritability; he complained of tachycardia and sometimes the heart action was "similar to a cog-wheel from which some cogs had been removed." He had hot flashes and perspired easily even in repose. During the last four months before admission he had lost weight (10 kgm.). Sleep had often been disturbed. There was no diarrhea, no vomiting nor anorexia.

Physical Examination. The patient was of ordinary stature. There was reduced subcutaneous tissue. The skin, especially in the face, was obviously flushed, warm and moist. The tongue was red and glossy. The eyes were lustrous in appearance, the lid-slits wide but without obvious exophthalmos; the signs of v. Graefe, Möbius and Stellwag were negative. The thyroid gland was somewhat enlarged, with even surface. Tremor was present of the type common in Basedow's disease. The heart was somewhat enlarged with tachycardia and a soft systolic murmur. When registering the blood pressure with the usual manchette an obviously positive Trousseaus sign appeared, the hand assumed the obstetrical position. Chvostek test was negative, but the peronaeus phenomenon was present and electrical examination showed an increased galvanic excitability. The temperature was sub-febrile and after a week afebrile. The pulse rate was 110 on admission and 75 on the last day in the clinic.

Laboratory Findings. The haemogramm showed: Hgb. 105 per cent, red blood corpuscles 5,390,000, white blood corpuscles 6200. Differential count: leucocytes 32 per cent (neutrophil 26 per cent, eosinophil 4 per cent, basophil 2 per cent), small lymphocytes 65 per cent, monocytes 3 per cent. The Wassermann reaction was negative. Fahreus (sedimentation of red blood corpuscles after one and after two hours) was 21/43. The general metabolic rate (after Krogh) was +62 per cent resp., +63 on the 11th of November. The calcium level (after Kramer and Tisdall, modified after Swaetichin) was 12.6 mgm. per cent. The amount of creatinine in the urine was from 0.52 to 0.70 gr. in 24 hours.

Treatment and Course. The patient was treated with Lugol's solution from the 12th of November (8 drops), from the 15th of November (10 drops), three times daily. During the last few days in the clinic no symptoms of tetany were observed.

Epicrisis. The case in question was that of a man aged 47 who previously was, on the whole, in good health. During 20 months before admission he presented symptoms of thyreotoxicosis, which became especially prominent during the last four months. In the clinic, he presented, on the one hand, the clinical picture of hyperthyroidism with the metabolic rate increased to more than 60 per cent and, on the other hand, positive symptoms of tetany.

TETANY CONNECTED WITH THYROID DISEASES

On the one hand, there are described in the literature some cases in which tetany has been observed in thyroid diseases. On the other hand, there are certain observations upon thyroid disorders that have developed during the course of tetany. Both groups of cases are briefly summarized below.

1. *Tetany observed in thyroid diseases.* The very uncommon cases in which tetany has occurred in myxedema are not dealt with here, since the tetany in these cases, according to Falta, has most often been impure (connected with epilepsy, etc.); but the observations upon tetany in goiter and in hyperthyroidism offer definite interest.

MacCarrison states that there are certain valleys in the Himalayas in which tetany is endemic among the women. In identically the same valleys endemic goiter is observed. The mothers of cretins and of children born with goiter commonly suffer from tetany during pregnancy. Mac-

Carrison himself reports a case in which tetany developed during pregnancy in a woman with goiter, who lived in a district in which goiter was endemic. When the patient moved to a non-goitrous district the tetany disappeared, reappearing again, however, after she returned to the former locality.

Falta suggests that there exists in Vienna and in Heidelberg a clinically characteristic kind of goiter, and that these very towns are special centers for the occurrence of tetany. He remarks, however, that there are also goitrous districts such as Steiermarkt and Tirol, in which no increased occurrence of tetany can be noted.

v. Frankl-Hochwart has described a condition, which he speaks of as "tetanoid," characterized by tachycardia, tremor, positive Chvostek reaction, goiter and vasomotor excitability. Presumably, he refers to some kind of thyreotoxicosis.

In hyperthyroidism, especially some years ago, cases were reported that were complicated by tetany. Thus Steinlechner describes a woman, aged 20, who had exhibited goiter for 10 years and tetany for one year; during this last year the goiter had obviously become toxic as there was exophthalmos, a positive sign of Graefe, tremor, tachycardia, diarrhoea, etc. Schultze reports the case of a girl, aged 16, who showed mild goiter, combined with tetany and excitation. Fraisseix observed a woman, aged 34, who suffered from thyreotoxicosis for many years (exophthalmos, positive signs of Stellwag and Moebius, a slight goiter, tachycardia, tremor) and in whom crises of tetany were observed. Jouffroy, cited by Fraisseix, mentions a woman, aged 25, presenting a thyreotoxicosis combined with several slight attacks of tetany in her arms. Hirschl observed a man, aged 18, the mother and the brother of whom had goiter, and who himself exhibited goiter, exophthalmos, positive signs of Moebius and Stellwag, tachycardia, positive signs of Chvostek, Trousseau and Schultze, and increased faradic and galvanic irritability. Jakobi observed a woman of 32, with a slight hyperthyroidism, who suffered from repeated attacks of tetany, though always in connection with pregnancy. The same author describes also three persons (mother, daughter of 15, son of 16) who had both goiter and tetany. Latzko, among six cases of osteomalacia observed in thyroidism, found two with tetany (two women aged 38 and 36, respectively). v. Gebele mentions cursorily a woman of 31 with Basedow's disease, combined with a positive Chvostek. Lublin describes a man with thyreotoxicosis, who presented a temporary tetany after the determination of the metabolic rate. Finally, Klose briefly remarks that tetany can appear in connection with Basedow's disease and that there has also been observed, in rare cases, the development of a chorea.

This review makes no claim to completeness but will suffice to illustrate the occurrence of tetany in association with thyroid diseases.

2. *Thyroid disorders observed in tetany.* An interesting observation was made by Falta and Kahn, who found in tetany, in its acute stage or

immediately after this stage, a slight but obvious enlargement of the thyroid gland, combined with moderate symptoms of hyperthyroidism, tachycardia, tremor, and excessive perspiration.

Thyroid disorders in tetany have also been observed by v. Frankl-Hochwart, who, among 26 cases of chronic tetany, found no less than 13 in whom there were slight symptoms of myxedema.

Falta from these observations assumes that there is during the acute stage of tetany an increase of the thyroid function which, later, in cases of chronic tetany, changes into a slight thyroid insufficiency.

3. *Treatment of tetany with thyroid products.* If it thus must be considered as established that tetany can appear in thyroid diseases and that thyroid disorders can occur during tetany, one must mention a third series of observations that also bring evidence of a connection between the two conditions mentioned. These observations have to do with the obviously beneficial, therapeutic results that are often obtained by using thyroid extracts in the treatment of tetany of parathyroid origin.

Because of the investigations of Kunde and of other authors (cited by McCullagh), it is generally conceded that animals with tetany die in a shorter time when they are not given thyroid extract.

In man, Kocher, Eiselsberg, Crile and others have used thyroid extract in cases of postoperative tetany, apparently with good results. It must, however, be remembered that, in these cases, as is also suggested by McCullagh, there were present not only disturbances of the parathyroid but also of the thyroid functions, and, because of this, the conditions have to be considered as rather impure.

Recently the therapeutic mechanism of thyroid extracts in tetany has been thoroughly studied in a case of postoperative tetany described by Albright, Bauer, Rossmeil and Aub (cited by Hunter). During two weeks thyroid extract was administered both by mouth and intravenously. The general metabolic rate rose from —14 per cent to +22 per cent, the blood calcium level, lowered by the operation to 6.7 mgm. per cent, was increased to 11.9 mgm. per cent, and the calcium excretion was elevated to three-fold its previous value. This increase of the calcium in the blood and in the excreta was still present six weeks after the last dose of thyroid extract, a surprising result, which was confirmed later. This effect upon calcium behavior could for certain reasons not be ascribed to the raised metabolic rate. The result is even more astonishing if we remember that the blood calcium level in hyperthyroidism is essentially normal (see below).

Finally, Stocker obtained obvious therapeutic benefit by treating postoperative tetany with parathormone combined with thyroxin. When this combination was made use of, only relatively small doses of parathormone (as a rule not more than 20 units daily) were required.

THE RELATION BETWEEN THE THYROID AND THE PARATHYROIDS

The beneficial result obtained with thyroid extracts in postoperative, parathyreoprivic tetany raises the problem of the functional relations that, according to our present knowledge, must be supposed to exist between the thyroid and the parathyroid glands.

Anatomically there are no constant changes in the parathyroids observable in cases of hyperthyroidism (McCallum, Benjamin, Kurokawa, McCullagh). In the cases of hyperparathyroidism hitherto described, on the other hand, no essential anatomical changes of the thyroid gland appear to have been observed; such changes were at any rate not to be noted in a case of osteitis fibrosa generalisata recently examined by Ask-Upmark, Kurokawa (cited by McCullagh) produced hyperparathyroidism in rats by transplantation of parathyroid glands; in 48 cases in which the glands were proved microscopically to have remained alive there were generalized atrophic changes in body tissues, the thyroid being no exception. After thyroidectomy certain authors (Gley, Vincent, Jolly and Klose) have reported different changes in the parathyroid glands; these observations, however, have never been confirmed (McCullagh, Klose). After parathyroidectomy, on the other hand, several authors (Edmunds, Lusena, Vassale and Generali; Halpenny and Thompson, and others) have observed hypertrophy of the thyroid.

Experimentally certain facts bearing upon the question under discussion have been acquired through work upon animals. Thus Minea and Radovici observed retarded regeneration of severed nerves in animals from which the thyroid and the parathyroid glands had been removed; this retardation could be overcome by administering thyroid and also by giving parathyroid hormone. Recently Stocker made some biochemical examinations (in dogs), which can be summarized as follows: When parathyroid hormone was given the blood calcium level rose, but the potassium and phosphorus levels remained undisturbed. If thyroxin was given contemporaneously with the parathyroid hormone the heightening of the calcium level was prevented. In dogs, from which the parathyroids had been removed, the blood calcium level fell almost 50 per cent and a marked elevation of the potassium level appeared, while the phosphorus level (as phosphates) was only moderately elevated; if now parathyroid hormone was given, the ion disturbance was overcome and the tetany was favorably influenced; if, instead of parathyroid extract, thyroxin was given, no noticeable effect upon the ion disturbance was observed. In hypo- or athyreotic dogs, from which the parathyroids were also completely or partially removed, there appeared, in addition to the disturbances of the calcium and potassium levels, a marked increase of the inorganic phosphorus (phosphates). The administration of larger doses of thyroxin rapidly diminished this hyperphosphatemia, and the calcium and potassium levels were restored to normal values; the symptoms of tetany would also disappear, if small quantities of parathyroid hormone were also given.

Clinically two observations are of especial interest—first, the observation, mentioned above, that parathyreoprive tetany can be beneficially influenced by the administration of thyroid extract (Kocher, Eiselsberg, Albright, Bauer, Rossmeil and Aub), the lowered blood calcium level being overcome, though administration of thyroid does not influence this level when values are normal (Hunter, Berencsy); secondly, the observation of the behavior of the so-called "parathyreogen reaction" in hyperthyroidism. By the parathyreogen reaction, according to Berencsy, is meant the increase of the calcium level observed 16 hours after the subcutaneous administration of 1 unit of parathormone per kilogram of weight of the body. The increase of the blood calcium level usually observed is between 0.5 and 1.5 mgm. per cent, but in hyperthyroidism the increase is considerably greater, 1.5-3 mgm. per cent, and this rise is to be regarded as characteristic for this disease (Csépai and Pelláthy, Berencsy). A similar augmentation of the blood calcium level has, however, also been noted in tetany (Berencsy). Csépai and Pelláthy conclude from the observation referred to that thyroxin sensibilizes the body to the parathyroid hormone. This suggestion agrees, as a matter of fact, very well with the therapeutic results obtained in cases of postoperative tetany through the use of parathormone in conjunction with thyroxin (Stocker, see above).

THE MINERAL METABOLISM AND THE THYROID GLAND

In consideration, on the one hand, of the relations stated above as existing between the thyroid and the parathyroids, and, on the other hand, of the central importance of the parathyroids for calcium regulation, the question arises whether or not there is any relation observable between the functions of the thyroid gland and the mineral metabolism of the body. Such a relation must undoubtedly be affirmed for two reasons: first, mineral metabolism is, in certain respects, responsible for the appearance of changes in the thyroid, and secondly, the mineral metabolism is markedly disturbed in cases of hyperthyroidism and of hypothyroidism.

1. *The importance of mineral substances for changes in the thyroid gland.* In the pathogenesis of goiter, there are, among the exogenous factors concerned, especially two that have, for many years, been supposed to be of central importance. One of these is a deficiency of iodine, the other an excess of calcium in the drinking water. The first factor need not be analyzed here; but it may be recalled that certain investigations during recent years have shown, first, that large amounts of iodine in the water of a certain district does not necessarily prevent the frequent occurrence of goiter (Liek), and, further, that in non-goitrous districts hyperplasia of the thyroid was not produced by feeding animals with a diet excessively poor in iodine (Hellwig). That a large amount of calcium in the drinking water may be important for the origin of goiter is a view suggested by several authors (McClelland, Bouchardat, Billiet, and others) more than 50 years ago. Later, the same theory was supported by other investigators, such as Pighini and Abelin, who demonstrated an antagonistic

effect of calcium and thyroxin in animals. Wilms and Repin eliminated the calcium from goitrous water, after which the water lost its power to produce goiter in animals. Geological investigations, carried on by McCarrison and Gilgit in India, showed that the drinking water in goitrous districts was derived from calcareous formations. Tanabe produced (in rats), on a diet poor in iodine, the largest goiters in animals that drank water that was rich in calcium. Hellwig, who cites the authors just mentioned, himself found first, that a diet rich in calcium but poor in iodine caused in rats a goiter that was characterized by parenchymatous, epithelial hyperplasia; secondly, that a diet rich in calcium and also rich in iodine gave rise to a diffuse colloid goiter; third, that on a diet poor in iodine but without any special amount of calcium, no thyroid changes occurred unless the diet used was extremely poor in iodine, in which case an atrophy of the thyroid gland occurred. According to Hellwig, a large amount of calcium in the drinking water is thus proven with certainty to be a positive factor in the pathogenesis of goiter; if there be at the same time a deficiency of iodine, the thyroid answers by epithelial, parenchymatous hyperplasia; if, on the contrary, there be a sufficiency of iodine, a diffuse colloid goiter is obtained.*

2. *The importance of the thyroid gland for the mineral metabolism.* The thyroid gland exerts a definite influence not only upon the general metabolic rate of the body but also upon certain more special metabolic functions, one of these being the regulation of mineral metabolism. In the first place, the importance of the thyroid hormone for the regulation of the water and salt metabolism of the organism has been established by Eppinger and has been developed by other authors; the special problems connected therewith are not discussed in the present paper, nor are the problems of iodine regulation. In the second place, several observations have been made that indicate the importance of the functions of the thyroid gland for calcium and phosphorus metabolism.

With regard to calcium metabolism it is necessary to emphasize that on any careful analysis, three factors must be considered: (1) the calcium level in the serum; (2) the calcium balance of the body, and (3) the nearer relations of the calcium in the serum. The calcium level in the serum is, as a rule, characteristically changed by disturbances of parathyroid function and when investigators turned their attention to the thyroid gland they examined first the calcium level in the serum and several reports of such studies are available. Recently, however, it has been evident that, as Hunter has said, it is not only the level of the calcium that is important, but also the rapidity and the direction of the calcium stream (out of the body or into the organism), that is to say, the calcium balance; of studies of this problem, only a few solitary publications have appeared. Finally, it has become clear that, besides the calcium in the serum, and the rapidity and the direction of the calcium stream, the more exact composi-

*Höser, however, in his careful study on goiter, denies the pathogenetic importance of calcium, postulated by Hellwig.

tion of the stream must be considered, on the one hand, and relations between the different fractions of calcium (ionized; non-ionized dialysable; non-ionized undialysable attached to colloids) and, on the other, the relations between the calcium and the other electrolytes.

1. *The blood-calcium level in hyperthyroidism.* The influence of the thyroid gland upon the blood-calcium level has been studied partly through clinical observations in cases of hyperthyroidism, partly through experiments upon animals.

The earlier clinical observations were somewhat divergent in results. Thus, Hall found the serum calcium level diminished both in cases of hyperthyroidism and in cases of hypothyroidism. Leicher observed in typical cases of hyperthyroidism a decreased serum calcium value (3 cases), in one case of hypothyroidism (myxedema infantum) a marked elevation of the calcium level, and in cases of non-toxic goiter normal or slightly increased values. Wade, who examined 11 cases of exophthalmic goiter and of toxic adenoma of the thyroid, found the calcium value to be consistently lowered in the untreated cases before operation (average value 8.3 mgm. per cent, while the average value of 10 normal persons was 10.1 mgm. per cent, whereas it became increased after operation. Castex (cited by Michaud) also found a decreased blood calcium level in cases of Basedow's disease. Montanari, on the contrary, has reported increase of the blood-calcium level (combined with decrease of the potassium level) in hyperthyroidism (8 cases), and decrease of the blood calcium level (combined, also here, with decrease of the potassium level) in one case of hypothyroidism. Herzfeld and Neuberger examined 19 cases of hyperthyroidism and found the calcium level in the serum normal in one-third of the cases, above or below the normal in two-thirds of the cases. McCullagh in 139 cases of hyperthyroidism and of hypothyroidism (the metabolic rates varied from —30 to +75 per cent) observed no definite changes in the serum calcium values; he stated, however, that cases in which there were symptoms of tetany were not included. Finally, Aub, Bauer, Heath and Ropes, after very careful analyses, assert that the calcium level in hyperthyroidism is essentially normal, and Hunter has recently confirmed this opinion. In several cases of hyperthyroidism examined in the medical clinic of Lund, the serum calcium was almost always found to be at the normal level. It would therefore appear that the calcium level is unchanged, at least in the majority of the cases of hyperthyroidism, even if, perhaps, exceptions are to be observed in certain cases.

After thyroidectomy for hyperthyroidism both Rabinowitch and McCullagh have noted a rather constant drop in the calcium level. Rabinowitch mentions that in his (26) cases there were no symptoms of tetany nor was any parathyroid tissue found in the excised tissue. Both of these authors believe that the decrease in calcium values depended, principally, upon traumatic insults to the parathyroid bodies (manipulation during operation, etc.). A postoperative increase of the calcium value was, on

the contrary, observed by Wade, as has been mentioned above. In the excellent study of Aub, Bauer, Heath and Ropes, no definite changes in the calcium level was found after subtotal thyroidectomy for hyperthyroidism, nor after administration of thyroid in cases of myxedema.

In animals, the findings as regards the serum calcium, after experimental thyroidectomy, are quite contradictory. Thus, Parhon found the level lowered after thyroidectomy in sheep, though no statement is made as to whether the parathyroid glands were also removed. In rabbits, Montanari found, on the contrary, the calcium value moderately increased after thyroidectomy. Finally, Botchkareff and Danilova removed the thyroid, together with the parathyroids, from sheep, and found the calcium level undisturbed by this operation. In consideration, on the one hand, of these divergent results, and on the other, of the difficulties in avoiding injury to the parathyroid bodies at such operations, it would seem that further investigations are desirable. The sex, the biological condition of the animal (whether pregnant or not), its herbivorous or carnivorous character, its age, the presence of accessory (or from the thyroid topographically separated) parathyroid bodies are factors that should be regarded.

2. *The calcium balance in hyperthyroidism.* In the earlier literature several observations bearing upon the relation of the thyroid gland to the calcium balance of the body have been recorded.

Experimentally, Bolaffio, Tedesco and Falta found that after the administration of thyroid in animals the phosphates in the stools were increased; they concluded that there must also be an increase of fecal excretion of calcium, corresponding to the augmented phosphorus output by the bowel. Parhon showed (1912) a marked loss of calcium in rabbits fed with lethal doses of thyroid; from this important observation it seems certain that the thyroid exerts a stimulating influence upon calcium excretion. That thyroxin increases calcium elimination in the urine has been shown by Schittenhelm.

Clinically, at the end of the 19th century it was established by v. Recklinghausen, by v. Koeppen and by Latzko that in exophthalmic goiter there can at times be observed a marked demineralization of the bony system. Scholtz, on feeding thyroid, found an increase of phosphorus excretion by the bowel, due to an augmented calcium elimination. Kummer (1917) published some observations upon calcium metabolism in a man of 42 who suffered from exophthalmic goiter. The observations were made over a period of 13 days; when the daily calcium intake was approximately 5 grams, the quantity of calcium in the urine was found to be normal, but that in the stools was materially increased. The author concluded that the mineral excretion was high but very irregular, both calcium and phosphorus losses being especially great, and he attributed the high fecal calcium to difficulty in absorption rather than to abnormal excretion. Castex, like Michaud, suggests that calcium elimination is increased in Basedow's disease.

More exact investigations of calcium and phosphorus metabolism in hyperthyroidism have, however, recently been made by Aub and his coworkers, Bauer, Heath and Ropes (1929); they studied the calcium, phosphorus and nitrogen excretion in a series of patients suffering from various thyroid diseases. Their results may be summarized as follows:

1. The calcium excretion in patients with exophthalmic goiter and in those with hyperfunctioning thyroid adenomata is increased markedly above the normal. This increase is far greater (average value +231 per cent) than the increase in the basal metabolic rate (average value +55 per cent).

2. The ingestion of thyroid by normal individuals likewise increases calcium elimination.

3. The calcium excretion in myxedema is markedly below that found in normal individuals.

4. A marked increase in phosphorus excretion was also found. This increase was quantitatively such as to suggest that most of the calcium excreted came from tertiary calcium phosphate in the bones.

5. This high rate of calcium elimination was not obvious in the blood, for essentially normal values for calcium and phosphorus were found in the serum.

6. X-ray evidence is presented, which indicates that osteoporosis may develop in the bones from prolonged hyperthyroidism.

7. The increased calcium excretion is not dependent upon the elevated metabolism alone, for in three out of four cases with high metabolism due to leukemia or fever, there was normal calcium elimination.

In addition to these points, mentioned by the authors in their own summary, they made other observations that are interesting.

8. The increased calcium excretion was, in thyreotoxic patients, about proportional in the urine and faeces.

9. The calcium excretion returned toward normal (1) in exophthalmic goiter on treatment with iodine and after subtotal thyroidectomy as the patient improved and the basal metabolic rate approached the normal; (2) in so-called hyperfunctioning adenomata after the adenomata were removed, and (3) in myxedema after administration of thyroid.

Finally, it should be mentioned that calcium is believed to exert a certain beneficial therapeutic effect both in patients suffering from Basedow's disease (Michaud) and in animals that are made hyperthyreotic (Abelin, cited by Michaud) since the irritability and the metabolic rate both are decreased.

3. *The more precise relations of the calcium in the serum.* It has been stated above that the calcium level is, in most instances, essentially normal in hyperthyroidism, though the calcium output from the body is increased. The question arises whether or not in Basedow's disease any change occurs in the relations on the one hand between the different frac-

tions that contribute to the actual calcium value, or, on the other hand, between the calcium and the other electrolytes.

The calcium in the blood of man is almost exclusively localized in the plasma. There are three fractions of calcium: (1) the ionized calcium, (2) the non-ionized, dialysable, inorganic calcium, and (3) the undialysable fraction attached to colloids. Authors are not wholly in agreement as to the values of the different fractions; it can be considered as established, however, that only a small part of the actual calcium value is present in ionized form, under normal conditions about 2.2 mgm. per cent (v. Euler). It has been supposed that the ionization of calcium is regulated by the parathyroid bodies (see Falta). As far as I know, however, no investigations have been made of the relations among the different fractions in hyperthyroidism; such investigations would be of interest.

The biological function of the calcium in serum depends, however, not only upon the actual value but also upon its relation to other electrolytes. Thus, it is a well-known fact that the ratio between potassium and calcium is of definite importance for certain biological conditions, e.g., the irritability of the heart and the excitability of the nervous system. In every investigation of the calcium, attention should therefore be paid also to the behavior of potassium. As regards hyperthyroidism, I have found only two authors who have dealt with that behavior—Montanari, clinically; Montanari and Stocker, experimentally. Further observations upon this would seem to be desirable. The astonishing changes of the potassium-calcium ratio observed after certain operations by Andrews and Reuterskiöld make such investigations important. Among the other inorganic ingredients of the blood, phosphorus should be studied. The phosphorus level in the serum is increased in hypoparathyroidism (the calcium level diminished); in hyperparathyroidism the phosphorus level is decreased (the calcium level augmented). In cases of hyperthyroidism, however, an essentially normal value of the serum prosphorus has been observed, but there is, nevertheless, a marked outflow of phosphorus from the body, though in proportion to the amount of calcium eliminated (Aub, Bauer, Heath, Ropes). It should also be mentioned that certain authors (Kocher, Payr, Morgenstern et al) have observed a beneficial effect from treatment by different phosphorus compounds in thyreotoxicosis. As to the chloride, the investigations of Eppinger indicate that the thyroid gland is of central importance for the storage of water and chlorides, especially in the subcutaneous tissues. As to iodine, several investigations have been made. It can be considered as established: (1) that the iodine level in the blood is increased in thyreotoxicosis (Veil and Sturm), and (2) that there are two fractions of iodine, one organic and undialysable, one inorganic and dialysable; when Lugol's solution is administered in hyperthyroidism, the former fraction decreases, the latter increases (for references, see Bier). Baldauf and Pincussen are studying the relations between iodine and bromine in Basedow's disease. Concerning the other electrolytes, no certain information seems to be available. On the whole, it would appear

that there are plenty of "white spots" on the map of the mineral metabolism in thyreotoxicosis.

Finally, we must never forget that the blood-calcium level, the calcium balance, and the relations of calcium to other electrolytes are questions that bear upon only one side of the metabolic disturbances in hyperthyroidism. The biological effect of the electrolytes is determined also by other metabolic conditions, the detailed relations of which in thyreotoxicosis cannot be analyzed here. Thus, according to Zondek, the biochemical changes in the colloid structures of the body are governed by at least three interconnected regulators: the visceral nervous system, the endocrine glands and the electrolytes.

DISCUSSION OF THE RELATIONS BETWEEN THYREOTOXICOSIS AND TETANY

The occurrence of tetany in hyperthyroidism, on the one hand, and the observation of undoubted symptoms of thyreotoxicosis appearing during tetany, on the other, make it rather probable that some pathogenetic connection exists between the two conditions. For an estimation of the pathogenetic relations, it must obviously be of first importance to establish the chronological development of the symptoms; we must determine whether the tetany or the hyperthyroidism is the primary condition.

I. *Tetany as the primary disability.* Cases in which tetany was the primary disorder and the symptoms of thyreotoxicosis appeared secondarily were first described by Falta and Kahn. It is possible that careful analysis would prove that a number of cases belong to this group. On attempting to explain the appearance of the hyperthyroidism in these cases, it is necessary to know the character of the tetany, and as yet we have no information on this point. It can be said, however, that if the tetany in question is not caused by a decrease of the blood calcium level, the symptoms of hyperthyreosis can hardly be understood in the present state of our knowledge. But, if the tetany is due to a lowering of the blood calcium, dependent upon a parathyroid insufficiency (see below), then the thyreotoxic symptoms would seem to be easily explicable on the ground that a hyperthyroidism develops as a compensatory process. There are, as a matter of fact, several circumstances that lend support to such an opinion. Thus, Falta and Kahn have emphasized that the hyperthyreotic symptoms appear during the acute stage of tetany or in immediate connection with it, that is, at a moment when the need of regulating mechanisms is greatest. Further, as has already been mentioned, there are the numerous observations of hypertrophy of the thyroid after removal of the parathyroid bodies. Again, the investigations of Csépai and Pelláthy have shown that the thyreotoxic organism is characterized by considerable sensitization to parathormone; in no other condition would such a hypersensibility be more desirable than in tetany of parathyroid origin, where the body is forced to make the best use possible of its remaining parathyroid powers. This reasoning may appear to be somewhat teleological. Finally,

however, it has been established that the thyroid hormone has no influence upon the serum calcium values, except in a single instance—when it is low, as in tetany (Bauer, Albright, Rossmeil, Aub). This fact is made use of therapeutically by those who administer thyroid in cases of tetany. Thyreotoxicosis as a compensatory phenomenon in tetany seems therefore to be a reasonable conception, though we must concede that it cannot be considered as proved. Slight myxedematous disturbances are, at times, observed in chronic tetany (v. Frankl-Hochwart); according to the view stated, we might perhaps consider these symptoms as phenomena pointing to exhaustion of the thyroid gland.

II. *Thyreotoxicosis as the primary condition.* When the hyperthyroidism is primary, later complicated by tetany, the pathogenetic relations between the two conditions must for the present be considered as unknown. It should, however, be remembered that the electrical neuromuscular irritability is generally increased in thyreotoxicosis; the appearance of tetany might, perhaps, be looked upon as an extreme form of a condition that is usually present in less degree in hyperthyroidism. For the pathogenesis of this form of tetany, there are, however, several possibilities that should be discussed.

1. In the first place, we should think of a possible relation to the parathyroids, the central significance of which for certain kinds of tetany has been thoroughly studied (see Salvesen). There are two ways conceivable through which the thyroid disability might influence the parathyroid glands: (1) mechanical and (2) hormonal. That the slight thyroid enlargement in Basedow's disease disturbs the parathyroids mechanically can, with certainty, I think, be excluded; if that were the case, we should see tetany much more often in cases of large, ordinary colloid goiters. That, on the other hand, a hyperthyroidism could cause a hypoparathyroidism hormonally cannot, with certainty, be denied; but it would appear strange in the light of what has been said above of the cases of tetany that are complicated by a secondary thyreotoxicosis: on the one hand, a hyperthyroidism would be the cause of a tetany of parathyroid origin, on the other hand, the thyreotoxicosis should contribute to the healing of the tetany produced! If, in spite of these apparent contradictions, a parathyroid tetany is still supposed to be caused by a thyreointoxication, it would have to be rather severe to permit of the recognition of its character. According to Salvesen, a blood calcium lowered below a critical level is a characteristic feature of the tetany of parathyroid origin. Objection to this statement may be that, on the one hand, the blood calcium level can be diminished by influences other than the parathyroid hormone, and on the other hand, that a parathyroid insufficiency can exist despite a blood-calcium value that is approximately normal. Thus, the former objection is validated by the observations of Berg, Hess and Sherman, who brought the calcium level down to 6 mgm. per cent (without obtaining tetany) by severing the splanchnic; further, by the recent investigations

of Nitschke, who found, among substances that can be isolated from the thymus and the spleen, one that evidently reduces the blood calcium. (The frequent occurrence of thymus hyperplasia in Basedow's disease may here be recalled.) Finally, by observations of the effects of other influences mentioned by Salvesen himself (high serum phosphates, low plasma protein, diet poor in calcium and vitamins). The second objection (that a hypoparathyroidism can be masked by a blood calcium level that is approximately normal) holds because of Collip's investigations, which have since been corroborated by other workers; Salvesen concedes the possibility as he states that it cannot be the actual value of calcium that determines the symptoms of tetany, since in the literature cases of evident hypoparathyroidism presenting an essentially normal calcium level have been reported. Thus, if the tetany is associated with an essentially normal serum calcium, we dare not, on that ground alone, exclude a parathyroid origin, especially not, perhaps, if the calcium value approaches the lower end of the normal scale. If, on the contrary, the level of the serum calcium is lowered, this symptom does not, in itself, prove the parathyroid origin of the tetany. We may add (1) that a lowered blood calcium must be rather rare in cases of hyperthyroidism since we know that the thyroid hormone raises a pathologically diminished calcium level; and (2) that if a lowered calcium level can be brought back to normal and the tetany made to disappear by using parathormon, this circumstance would support the view of a hypoparathyroidism as the cause of the tetany.

2. In the second place, it is to be remembered that there is in hyperthyroidism a considerable outflow of calcium from the body (Aub, Bauer, Heath, Ropes). Even if, under normal conditions, a definite relation exists between the calcium of the blood and that of the tissues, the same equilibrium could scarcely be maintained in a disability through which the "calm" calcium level in blood is converted into a rapid stream, flowing out of the organism. Thus, it is possible that the calcium content of the nervous system is decreased in hyperthyroidism, in spite of the fact that the blood-calcium level is usually normal. Moreover, as was pointed out above, the bony system is markedly demineralized in hyperthyroidism. It must certainly be conceded that most of the calcium eliminated in hyperthyroidism is derived from the bones, since no other tissue is capable of delivering the large quantities observed. There is, however, no evident reason why, corresponding to the osteoporosity of the bones, there should not be a similar decalcification of other tissues, including the nervous system. As the excitability of this system seems to be determined by the balance existing between calcium and certain other ions (e.g., potassium),* it is obvious that an excessive calcium outflow should produce tetany. Hence, we should meet with tetany especially in those cases of hyperthyroidism in which there is a rapid diminution of the calcium stores of the body, though this does agree very well with the case described above, in

*See note below on the phosphorus-calcium equilibrium, which does not appear to be disturbed in Basedow's disease.

which the thyreotoxicosis was rather acute and of high grade. Against the hypothesis mentioned, two objections may be raised: (1) the objection that thus far the calcium content of the nervous system in hyperthyroidism has not been studied nor are we acquainted with the behavior, in thyreotoxicosis, of inorganic substances other than calcium and phosphorus; the objection raised demands, therefore, further investigations; and (2) the objection that there is another disability, the hyperparathyroidism, that is, the osteitis fibrosa generalisata of Engel-Recklinghausen, characterized by a considerable outflow of calcium from the body, but which, unlike thyreotoxicosis, is accompanied by markedly hypodynamic symptoms. This second objection cannot, however, be considered to be very serious, for two reasons. On the one hand, the disturbance of the mineral metabolism is quite different in the two conditions in question; in Basedow's disease, the blood-calcium and the blood phosphorus levels are essentially normal, the augmented calcium and phosphorus elimination occurring by way of both the urine and the faeces; in Engel-Recklinghausen's disease, the blood calcium is considerably increased, the blood phosphorus decreased, and the increased calcium and phosphorus outflow occurs only by way of the urine. On the other hand, the investigations of Albright, Bauer, Ropes and Aub indicate that the primary effect of the parathyroid hormone is to increase phosphorus excretion, and this increase is greater than can be explained theoretically by a calculation of the phosphorus liberated along with calcium and nitrogen, the excreted phosphorus being partly derived from the body fluids. Since the relation between calcium and phosphorus is of central importance for the irritability of the nervous system (György and others) the changes in this relation caused by hyperparathyroidism results in a decreased neuromuscular excitability.

3. Tetany due to alkalosis can be produced either by pyloric obstruction (loss of hydrochloric acid through vomiting), or by hyperventilation (loss of carbonic acid through hyperpnoea). The blood-calcium level is, in these conditions, normal. Vomiting is a common symptom in exophthalmic goiter; further, Cameron and Carmichael caused death from tetany by feeding thyroid extracts to rats, and considered the tetany produced to be due to hyperpnoea. Yet it seems unlikely that an alkalosis commonly plays a part in the pathogenesis of the tetany observed in Basedow's disease; and the following considerations can be urged against the view:

(a) As to the tetany being due to vomiting, it should be pointed out (1) that tetany is observed also in cases of hyperthyroidism that manifest no gastrointestinal symptoms, and (2) that in Basedow's disease achylia is common, in which event vomiting does not cause loss of hydrochloric acid.

(b) As to the tetany being due to hyperpnoea, it must be conceded that the respiration of these hyperthyreotic patients is animated and that the oxygen consumption is considerably increased, as shown by the accelerated metabolic rate. But that does not prove that hyperventilation of

the tissues occurs or that there is an alkalosis present. On the contrary, it has been suggested that the primary effect of thyroxin is to increase anoxybiotic decomposition and that the augmented need for oxygen is a secondary phenomenon, necessary for the oxidation of the great increase in lactic acid due to the former process (Haffner, König and others). There are, as a matter of fact, several observations that demonstrate a great increase of lactic acid in the blood of persons suffering from hyperthyroidism (Bier, Eichler and Sanders, König). The thyreotoxic organism is not able either to resynthesize or to neutralize the lactic acid, but is forced to make it harmless through oxidation. On consideration of these facts, which have also been established experimentally (see König), it would seem necessary to remain very critical of the suggestion of Hollo and Weiss (cited by Falta) that there is an alkalosis in Basedow's disease. On the contrary, the investigations upon the production of lactic acid, briefly mentioned above, seem to make probable the existence of a certain degree of acidosis, or at least of a disturbed buffer equilibrium in favor of an acidity (vide infra). This agrees with the observations gained in experimental animals fed with thyroid, in which Parhon, Cahane and Orenstein have observed a diminishing of the alkaline reserves, as well as with the clinical investigations of Saida (cited by Delaunay), in which the hyperthyroidism was found to exert an acidotic effect. It may also be remembered that certain clinicians use alkalies for the treatment of thyreotoxicosis, apparently with beneficial results (Berg; see König). It is necessary, however, to remember that the discovery of a lactacidemia does not, in itself, prove the existence of an acidosis. Thus Frank, Leiser and St. Weiss, in an interesting study, have shown that the alkalosis obtained by hyperventilation is associated with an increase of lactic acid in the blood and of acetone bodies in the urine, an increase that should be looked upon as a compensatory phenomenon against the alkalosis. On the other hand, the finding of a normal pH in the blood does not prove the absence of an acidosis, for the kidneys are capable of eliminating the produced surplus of acids. In any careful analysis of the problem touched upon here, it is therefore necessary, not only to make a thorough investigation of the alkali reserve in the blood, but also to make determinations of the acids excreted in the urine. Studies of the total acid-base metabolism in hyperthyroidism and in myxedema are in progress by Aub and his coworkers. For the present, however, we must consider the possibility that an alkalosis plays a rôle in the pathogenesis of the tetany observed in thyreotoxicosis as rather unverified, even if, for at least certain cases, this possibility dare not be absolutely denied. Thus, it has been shown by Lublin that tetany is, at times, in Basedow's disease, really due to a hyperventilation, when the respiration, for any reason, becomes accelerated, for example, when the passage of air through the respiratory tract is disturbed, as when the nose is compressed during measurement of the metabolic rate.

4. The view that tetany is due to autointoxication with guanidine, depending upon a deficiency of the parathyroid glands, has been severely criticized by several authors (Greenwald, Salvesen, Spiegel, Collip and Clark, Berençsy and Zinhobel). Our present knowledge of this subject may here be briefly summarized. In the first place, the supposed importance of deficiency of the parathyroid glands for guanidine poisoning must be denied, since Collip and Clarke could not prevent guanidine intoxication (in dogs) by large doses of parathyroid hormone. That, nevertheless, some relationship exists between guanidine and tetany seems certain. Thus, guanidine can produce, in animals tetany-like conditions (Paton and others) or, at least, an increased electrical irritability (Berençsy and Zinhobel). Furthermore, disturbances of the guanidine and of the creatinine metabolism have been observed in tetany (Koch, Paton, Burns and Shape, Henderson, Palladines and Grilliche). Finally, in guanidine intoxication, some authors have described changes of the blood electrolytes similar to those often observable in tetany, including diminished calcium level and increased phosphorus level (Watanabe, György and others); other investigators, however, have failed to confirm these observations (Nelker, Salvesen, Collip and Clark, Berençsy and Zinhobel). In man, the creatinine in the urine is to be considered as a derivative of the endogenous protein metabolism, presumably coming from guanidine compounds. If so, the quantity of creatinine in the urine must be influenced by the rate of protein metabolism in the tissues and one would expect a large amount of creatinine in the urine in a disease characterized by such an exaggerated protein metabolism as is met with in hyperthyroidism. But, on the contrary, the urine in Basedow's disease contains remarkably small amounts of creatinine (Forschbach and others). In my own patient, described above, the quantity of creatinine excreted in 24 hours was obviously decreased, despite the considerably increased general metabolic rate. It must, therefore, be considered as possible that the protein metabolism in thyreotoxicosis, as far as the guanidines are concerned, "runs off the line," which certainly does not prove that a guanidine intoxication must be the result. Further investigations are here necessary. It is a curious fact that the early theory of autointoxication as the cause of tetany assumed along with other suggestions, that the thyroid gland was responsible for the poison production (Vassale and Generali). In summary, it may be said that there are certain undeniable relations between guanidine and tetany, that the parathyroid glands do not appear to be concerned in these relations, and that possibly guanidine metabolism is disturbed in exophthalmic goiter.

The pathogenetic relations between thyreotoxicosis and tetany, mentioned above, may now be summarized. It must be conceded that we cannot, at present, reach conclusions that go far beyond probabilities and mere suppositions. It is, however, of central importance to establish the chronological succession of the two conditions in question. In certain cases, the tetany is, without doubt, the primary disability and the thyreo-

toxicosis must be considered to be a secondary phenomenon, perhaps of compensatory importance. In other cases, the hyperthyroidism is the primary condition and is complicated by the appearance of tetany. The cause of this tetany is, at present, unknown; possibly it may be complex. The electrical neuromuscular irritability is generally increased in thyreotoxicosis, and because of this the tetany that appears may, perhaps, be looked upon as an extreme form of the conditions ordinarily present in some degree. That an alkalosis is the cause of this tetany is to be doubted. It is, further, improbable that a parathyroid insufficience can be the only cause. It is not impossible that certain disturbances of endogenous protein metabolism may play a part. It is possible, and perhaps probable, that the extremely increased calcium excretion by the body may be of some importance. It remains to be established whether or not the hyperplasia of the thymolymphatic system plays any rôle, a topic that will be discussed below. Further investigations of all these matters are obviously necessary.

SOME OTHER PROBLEMS IN HYPERTHYROIDISM

There are certain other problems connected with hyperthyroidism, which seem worthy of analysis, particularly in the light of our newer knowledge of mineral metabolism. Three of them will be briefly discussed here: (1) the osteomalacia, (2) the thymus hyperplasia, and (3) the postoperative deaths.

Osteomalacia and tracheomalacia. The changes of the skeletal system in thyreotoxicosis have already been referred to above. The decalcification and the brittleness of the bones have been demonstrated clinically as "osteomalacia in Morbus Basedowi" by v. Recklinghausen, Koeppen, Möbius, Hofmeister, Hirschl, Latzko, Schickele, Bernhardt and others; they were studied roentgenologically first by Kummer, later by Bernhardt, v. Jaksch and Rothy, Aub et al., Plummer and Dunlap, Hueper and Hunter, and anatomically by v. Recklinghausen (1891), Askanazy, v. Jaksch and Rothy, Koeppen, and Hunter. The observation of Holmgren that juvenile subjects of hyperthyroidism show a remarkable, rapid growth should also be remembered. This observation gains increased interest through the investigations of György, who showed that the subepiphyseal layer of the spongy structure represents, in the calcium metabolism, a special store of calcium, which is particularly easy to mobilize. The great importance of this very region for growth, on the one hand, and the increased calcium elimination in hyperthyroidism, on the other, are facts that can be brought into connection with Holmgren's investigations, as can perhaps also, our newer knowledge of the phosphatases. These phosphatases are enzymes that are of importance for ossification; they are present in increased amounts in the plasma in certain generalized bone affections (especially in the osteitis deformans of Paget), as well as in hyperthyroidism (Kay, Hunter); in the growing skeleton, they are localized especially in the centers of growth (Kay, Hunter).

As to tracheomalacia, it is a fatal complication met with in rare instances in association with goiter. It is as yet uncertain to what degree this cartilaginous disorder is due to a mere compression atrophy, caused by the enlarged thyroid gland. In addition to this mechanical factor, obviously existent especially with large goiters, we must, however, also consider the generalized emaciation and the decalcification of the supporting tissues always associated with the toxic goiters. Certainly, it must be conceded that the tracheal rings may not, off-hand, be compared directly with the bony system. The possibility that the immediate environmental relation of the tracheal cartilages to the thyroid gland may be of importance (through greater exposure to lymphatic influences) should not be forgotten.

The thymus hyperplasia. The significance of the thymus hyperplasia belongs among the classical problems of Morbus Basedowi. For a long time only one fact was known, namely, that enlargement of the thymus is common in hyperthyroidism, especially in the severe cases, despite the general emaciation, which might *a priori* be expected to favor the involution of the thymus. But a whole series of hypotheses have been suggested. Thus, certain authors have looked upon the thyroid- and the thymus-enlargement as coordinated phenomena, due perhaps to constitutional factors. Others have regarded the thymus hyperplasia as primary and the thyroid changes as secondary. Others again have looked upon the enlargement of the thymus as a phenomenon secondary to the increased thyroid function. That constitutional factors play an important rôle in the pathogenesis of Basedow's disease is not to be doubted, nor should the possibility be denied that certain tumors of the thymus may perhaps give rise to a clinical syndrome similar to that of hyperthyroidism (Klose). Nevertheless, the view that the thymus-hypertrophy is secondary to the thyroid changes has attracted most attention (see Löwenthal). This theory, however, includes two quite different possibilities:

(1) Synergistic action of thyroid and thymus, the changed thymus exacerbating the thyroid intoxication; and

(2) An antagonistic action of thyroid and thymus, the enlarged thymus exerting a compensatory influence upon the thyroid intoxication.

Among the observations cited in support of the former opinion may be mentioned first those of Bircher, who implanted thymus tissue from man in the abdominal cavity of dogs and produced in five cases, tachycardia, tremor, exophthalmus and goiter; if the thyroid gland were then removed, the animal did not exhibit the chronic cachexia strumipriva that usually follows thyroidectomy but developed toxic symptoms and died in a short time. The observations are interesting, and yield some support also to the theory of a thymogenous Basedow (in the sense of Hart), but the experiments require, as Falta also remarks, repetition, since v. Gebele was not able by similar experiments to produce any thyreotoxic symptoms in dogs. Again, it has been asserted that a morphological hyperplasia of

the thymus occurs if the thyroid gland is removed (Hofmeister, Gley, Biedl and others), and also that an enlargement of the thyroid gland occurs after thymectomy (Béclard, Matti, Klose). Later, more careful investigations indicate that these observations were inaccurate or wrongly interpreted; the thyroid changes after thymectomy are in dispute and the removal of the thyroid obviously results in an involution of the thymus (Tatum, Marino, Manley, Baumann). This last observation corresponds well with human conditions, since in cases of human myxedema there is no evidence of retardation of the physiological involution of thymus (see Löwenthal). Finally, it has been asserted by certain authors that amelioration of the symptoms of Basedow's results from removal of the enlarged thymus alone (Capelle and Bayer, Garré and others); these surgical observations, however, have not withstood rigid critical analysis (see v. Gebele and Löwenthal).

On the other hand, there have been various observations that suggested an antagonistic relation between the thymus and the thyroid—the possibility of causing thymus enlargement by administration of thyroid; the results of certain experiments in which thymus was fed to animals; the effects following experimental thymectomy; the therapeutic value of thymus administration observed by certain authors in exophthalmic goiter.

1. Thus, on feeding thyroid to rabbits over long periods (weeks and months), there was observed, despite general emaciation, no involution of the thymus (Utterström). Enlargement of the thymus occurred in rats that were fed with thyroid (Kliwanskaja-Kroll). If pregnant guinea pigs were fed with thyroid, their young exhibited obviously larger thymus glands than did the controls (Hoskins). Courrier, who fed rats and young cats with thyroid, found that, if the other food were insufficient, the animals died inanitio modo, exhibiting atrophic thymus glands, but, if the food were sufficient, the thymus glands became enlarged, facts that are suggestive of a special influence from the thyroid. Finally, Löwenthal remarks, citing Messerli and Coulaud, that rats in different places have thyroids that differ in size, and the animals with large thyroids also had large thymus glands.

2. Further, in tadpoles, metamorphosis was accelerated and growth was retarded by thyroid, whereas the contrary was the case when thymus was administered. Sklover fed male white mice with thymus, with thyroid, and with thymus-thyroid: the weight rapidly decreased on thyroid feeding; it was at first constant, and later increased on thymus feeding; it was essentially constant in the thymus-thyroid animals. The production of carbon dioxid was considerably increased in the thyroid-fed animals; it was at first constant, and later decreased in the thymus-fed mice; and in the animals fed with both thymus and thyroid it was at first increased, and later became constant on the original level. Similar observations have been made by v. Gebele, who worked with mice and guinea pigs: the weight decreased, often considerably, in the thyroid-fed animals, increased

in controls, and increased still more in the animals fed on thymus; the basal metabolic rate was increased if thyroid was given, and was decreased in the other animals, though in the animals fed on thymus there was a brief increase at first. Both the authors mentioned conclude that the thymus and the thyroid are antagonists; but the value of their investigations is reduced by the fact that no extracts from other organs were used. Krizenecky fed pigeons with thyroid, with thymus, with thyroid + thymus, and with dried veal (as a control); he found that the thyroid effect upon weight and upon growth was prevented by the administration of thymus.

3. Certain observations after experimental thymectomies have been cited in favor of the view that the thymus influences metabolism and the skeletal system. Friedleben (cited by v. Gebele) found that the consumption of food was increased in animals from which the thymus had been removed. According to Ruchti (cited by Sattler u. Borchardt), the respiratory metabolism was not changed in animals from which both thyroid and thymus had been removed; it was decreased, however, when only the thyroid was removed. Nyffenegger (cited by Sattler u. Borchardt) found the effect of heat puncture to be decreased after thyroidectomy, considerably increased, however, if thymectomy was also carried out. As to the bony system, Basch was able to show that animals, with thymus removed, exhibited a greatly increased calcium excretion, more fragile bones that were easily fractured and defects in callus formation, which was retarded, often resulting in pseudarthrosis. Sinnhuber, on the contrary, found no changes in calcium elimination after thymectomies, but Bracci found it to be increased; the calcium content of the blood was augmented, that of the bones, nerves and muscles diminished, if the thymus were removed. Klose and Vogt assert that on removal of the thymus in dogs, there was increased hunger, loss of weight, and changes in the skeletal system similar to those described by Basch. Not all authors, however, have been able to confirm these observations.

4. Finally, the therapeutic results, which were at times obtained by administration of thymus in cases of exophthalmic goiter, are remarkable. The method was introduced by Owen (at first incidentally) and has later been applied by a large number of authors (see Sattler a. Borchardt), apparently with beneficial results. Other authors, however, had divergent experiences. There is, so far as I know, only one author, Libesny, who determined the metabolic rate in connection with the therapy in question; he found this rate to be decreased when thymus tablets were fed in Basedow's As small doses of iodine were given contemporaneously, however, the experimental auspices were not quite pure.

The observations referred above can be summarized as follows:

1. By implantation of human thymus on dogs, symptoms similar to those by Morbus Basedowi are sometimes (Bircher) but not always (Gebele) obtained.

2. If the thyroid gland be removed in animals, there results an involution of thymus.

3. In myxedema, no retardation of the physiological involution of thymus occurs.

4. By administering thyroid to animals, the involution of the thymus can be retarded and often replaced by an enlargement.

5. Thymus and thyroid exert an opposite influence in certain conditions, if administered to animals.

6. After experimental thymectomy, certain results are obtained as to the relations of the metabolism and the bony system, which seem to make an antagonistic position to the thyroid gland probable.

7. If thymus be administered in cases of Morbus Basedowi, an improvement can sometimes be noted.

8. An enlargement of the thymus is common in Morbus Basedowi, especially in the severer cases.

It thus appears that an antagonistic relation exists between the thymus and the thyroid gland. Against this opinion are, however, first, the investigations of Bircher (point 1), which seem to be rather mysterious, diverging from all the other observations; this objection cannot, however, for the present, be refuted. Secondly, against the supposed antagonism, it has been urged that several cases of Basedow's disease have not presented any enlargement of the thymus, that the patients may die without operation, and that post-operative deaths occur with increasing symptoms of intoxication. This latter objection will be referred to later; to the other two, it may be answered that a compensatory thymus hypertrophy can obviously be missing in cases of thyreotoxicosis when the course is so rapid that there is not time for reactive phenomena to develop, and that the supposed character of the thymus enlargement does not exclude the possibility that the compensation may be insufficient.

The contrary theory of a synergism of the two glands in question is to a certain degree supported by the investigations of Bircher; the results of these are in conflict, however, with the majority of the observations cited above, and they meet with the difficulty of explaining the acute exacerbation of the intoxication that may be observed after removal of the thyroid gland.

Between these two general theories, a decision has, accordingly, thus far been rather difficult; the only facts that we know with certainty are that thymus hypertrophy is common in Basedow's disease, especially in the severe cases, and that this hypertrophy is, probably, secondary to the thyroid changes. On the whole, it is evident that the successful investigations of certain other problems of thyreotoxicosis (such as iodine-therapy, etc.) have dominated interest during late years, and it is doubtless because of this that most of the papers dealing with the thymus enlargement date back to an earlier era.

Recently, however, Nitschke has succeeded in isolating from the thymus two different substances; one of them lowers the blood-calcium level, the other, quite different and distinguishable from the former, decreases the inorganic blood phosphorus sometimes more than 50 per cent. These two substances are present also in the spleen and in the lymphatic glands but could not be found in other tissues examined. The calcium lowering substance was without influence upon the general metabolic rates. The phosphorus lowering substance, on the contrary, constantly decreased the rate of metabolism both in normal animals and in animals in which the metabolic rate had been increased by thyroid feeding. This decrease of the general metabolism could only be obtained, however, when the actual extract from thymus and spleen that diminished blood phosporus was used, not, however, if certain other extracts were injected (Schneider and Nitschke). It should be mentioned that a lowering of calcium was obtained also by Reiss, Winter and Halpern by the use of certain extracts from the thymus or the spleen, extracts which, however, evidently increased the calcium content of the bony system; an antagonistic relation to the thyroid gland was thus demonstrated.

These investigations appear to be quite convincing, though the objections may be that the hormonal nature of the related substances cannot for the present be considered as established, and secondly that the results mentioned were obtained, for the more part, in animals because of which caution must be exercised in deciding as to their applicability to human conditions. With these reservations, and pending control by further studies, the investigations of Nitschke and Schneider would seem to be of definite importance. They yield objective foundation for certain observations made earlier upon an antagonistic relation between the thyroid and the spleen. Thus, Asher obtained a characteristic histological picture of the bone marrow on injecting sodium nucleinate; this reaction picture disappeared after removal of the thyroid but reappeared if the spleen were then removed. Further, it was established that the regeneration of the blood was decreased if the thyroid were removed; after splenectomy, the regeneration returned to normal (Asher, Nakao). Grafe and Mark were able to lower the metabolic rate in Morbus Basedowi by feeding spleen. Tanaka, as a result of his experiments in animals, suggests that the spleen and the thyroid exert antagonistic influences upon the level of lactic acid in the blood. See, also, Schliephake. Further, and of still greater importance, they seem to offer possibilities for a better understanding of the reciprocal play between the thyroid and the thymolymphatic system in hyperthyroidism; thus, the thyroid increases the metabolic rate; and it is possible that the thymolymphatic system decreases the rate. This view would seem to afford, on the one hand, a biological explanation of the enlargement of the thymus and of the spleen in thyreotoxicosis as a compensatory phenomenon and, on the other hand, it helps to elucidate certain clinical peculiarities of hyperthyroidism. The enlargement of the spleen by Basedow's disease is suggested as least by several authors (see Henke-

Lubarschs Pathology). A patient with hyperthyroidism, attended in the medical clinic of Lund, claimed abdominal pains and for this reason had been laparotomized before in another hospital; at operation there was found a considerable enlargement of the spleen, but nothing else pathological was found in the peritoneal cavity. Thus, it is a remarkable fact that Basedow's disease is almost never observed in young children, though it is frequently met with during the period of involution of the thymolymphatic system (Nitschke). Again, the possibility should be kept in mind that perhaps the tetany sometimes observed in hyperthyroidism may be due to the assumed reactive hyperfunction of the thymus; in favor of this view, it will be recalled that the extracts of the thymus and spleen described lowered the calcium level in the serum, and that the animals into which the extracts were injected exhibited tetany-like conditions (increased electrical irritability, spasms and, frequently, exitus lethalis); moreover, they showed the same symptoms as appear on injection of extracts from the urine of spasmophile children (Nitschke). If, in a case of Basedow's disease, a lowered blood-calcium level be observed, it is conceivable that the thymolymphatic system has gained a temporary preponderance in the balance against the thyroid (which tries to keep the level normal); at any rate, in such cases, as has been emphasized above, it is not permissible to think only of a primary parathyroid insufficiency. Furthermore, the therapeutic effect of thymus administration in cases of thyreotoxicosis, observed by certain authors (see above), would seem to find its probable explanation. The observations of Lublin and others, who found that the metabolic rate is not, at times, increased in thyreotoxicosis, or, at least, is not increased to the degree that would be expected, would seem less mysterious. Finally, the characteristics (mentioned above) of the thymus hyperplasia that is secondary to the thyreotoxicosis help us to understand the postoperative deaths.

The postoperative deaths in Morbus Basedowi. The deaths after ordinary operations for hyperthyroidism (subtotal resections) are, as is well known, partly due to pneumonias, partly (probably in the majority of cases) to an intoxication that is clinically characteristic. Whether this intoxication is due to an overwhelming of the organism with thyroid secretion, liberated by the operative manipulations, or is, on the contrary, due to a relative deficiency of thyroid hormone, caused by removal of too much of the gland, has for a long time, been a debated question. Recently, however, Arthur Bier, through studies of the iodine metabolism in Basedowian patients, in which the operation of subtotal strumectomy had been performed, has made it seem probable that the severe and often fatal postoperative reactions depend upon a temporary decrease of the thyroid secretoin in blood. The results of the investigations of Schneider and Nitschke are, as a matter of fact, presuming that we have to deal with hormonal substances, corresponding very well to this view; for if most of the thyroid be removed, the thymolymphatic system will gain preponder-

ance and the general metabolic rate will decrease abruptly. It will be obvious that, according to such a view, the postoperative reaction must be especially severe in cases in which the thymolymphatic system has been considerably involved (cases with thymus hyperplasia!) and in which the resection of the thyroid has approached total thyroidectomy. Further, there would exist, at least theoretically, the possibility that in the cases in which postoperative tetany appeared, this could be due not only to the operative maltreatment of the parathyroids but also to the calcium-decreasing function of the thymus, which would become influential on removal of the thyroid gland. Finally, in addition to iodine therapy, it is obviously necessary in the postoperative stage to supply the body with a sufficient amount of oxygen, for two reasons: first, because the tissues, even before operation, have been subjected to abnormal metabolic conditions (with increase of lactic acid, etc.); and, secondly, because the general decrease of the metabolic rate after operation must of necessity lead to at least a relative anoxaemia of the tissues. The modern oxygen chambers may here perform a useful function.

Whether or not the investigations of Nitschke can assume importance for diagnosis, must remain undecided until further researches are carried out. That determinations of the calcium and phosphorus levels before operation could give information of value regarding the relations of the thymolymphatic system seems improbable since the regulation of these levels is rather complicated. On the other hand, the possibility that such determinations might give objective clues as to the degree of assumed postoperative thymolymphatic intoxication existent may well be borne in mind. It should not be forgotten, however, that such determinations are subject to several sources of error (including, for example, the operative maltreatment of the parathyroids); more valuable information is to be expected, perhaps, from determinations of the basal metabolic rate.

GENERAL COMMENTS UPON THE MINERAL METABOLISM IN HYPERTHYROIDISM

In the present paper, the mineral metabolism (especially the behavior of calcium) has been placed in the center of the discussion. It must, however, be definitely emphasized that we do not believe the calcium to be any philosopher's stone for the solution of the problems of thyreotoxicosis. In hyperthyroidism we have to deal also with disturbances of other metabolic processes, for example, the carbohydrate and the protein metabolism. Nevertheless, the mineral substances are of definite importance for the course of the biochemical processes in the body and they exert their influence in immediate connection with the visceral nervous system and the endocrine glands. It therefore seems legitimate to discuss the problems of the mineral metabolism in one of the most characteristic endocrine disabilities with which we are acquainted. A sound basis for the discussion of these problems has, for the first time, been provided by the researches of Aub, Bauer, Heath and Ropes, of Hellwig, of Nitschke and of other

authors. Starting with these fundamentals, further investigations should be undertaken in order to build up an exact knowledge of the rôle played by the electrolytes in Basedow's disease.

SUMMARY AND CONCLUSIONS

1. A case in which tetany appeared in the course of Morbus Basedowi is here reported, together with a brief review of analogous observations in the literature. The problem of the relation between the two conditions is presented for analysis.

2. Our newer knowledge of the mineral metabolism in hyperthyroidism can be summarized in two theses: first, the calcium content of the blood is possibly of importance for the development of thyroid changes; second, there is, in hyperthyroidism, an exaggerated excretion of calcium and phosphorus by the body, in spite of the maintenance of the normal blood levels of these substances.

3. The pathogenesis of tetany in Morbus Basedowi is discussed, the author arriving at the conclusion that there are two varieties. In one variety the tetany is without doubt the primary condition and is caused probably by parathyroid insufficiency, whereas the thyreotoxicosis is to be considered as a secondary phenomenon, perhaps in certain respects of compensatory significance. In the other variety the hyperthyroidism may be the primary disability, which is complicated by the appearance of tetany. The cause of this second variety of tetany must for the present be considered as unknown; alkalosis can scarcely be the cause; parathyroid insufficiency cannot be the only cause; and certain metabolic disturbances in thyreotoxicosis may, it is believed, favor the development of this tetany. Further investigations on each of these points is necessary.

4. The osteomalacia, the tracheomalacia and the increased growth of the juvenile skeleton in hyperthyroidism are touched upon, and thymus-hypertrophy is discussed. In consideration of the recent investigations of Nitschke and Schneider, which, however, require supplementation, the author arrives at the conclusion that the hyperplasia of the thymolymphatic system may be regarded as secondary to the thyreotoxicosis, and certain practical consequences of this view are discussed.

REFERENCES

Abelin, T.: Biochem. Ztschr. **199**: 72. 1928.
Albright, Bauer, Rossmeil and Aub: To be published (cited by Hunter. 1930.)
Andrews, E. and K. Reuterskiold: Ann. Surg. **92**: 786. 1930.
Anselmino, K. J. and F. Hoffman: Klin. Wchnschr. **9**: 1768. 1930.
Asher, L.: Klin. Wchnschr. **9**: 73. 1930.
Askanazy: Festschr. f. Jaffé (Vieweg u. Sohn, Braunschw.). 1901.
Arb. a. d. Geb. d. path. Anat. B. **4**: 398. 1904.
Ask-Upmark, E.: Acta med. Scandinav. **74**: 284. 1930.
Aub, J. C., W. Bauer, C. Heath, M. Ropes: J. Clin. Investigation, **7**: 97. 1929.
Baldauf, L. and L. Pincussen: Klin Wchnschr. **9**: 1505. 1930.
Barr, O. P. and H. A. Bulger: Am. J. M. Sc. **179**: 449. 1930.
Berencsy, G. v.: Klin. Wchnschr. **9**: 1213. 1930.
Berencsy, G. v. and K. Zinhobel: Klin. Wchnschr. **9**: 1503. 1930.
Berg, B. N., A. F. Hess, E. Sherman: J. Exper. Med. **47**: 105. 1928.

Bernhardt, H.: Deutsche Med. Wchnschr. **53**: 1082. 1927.
Bier, A.: Klin. Wchnschr. **9**: 819. 1930.
Billiet: 1853 (cited by Hellwig, 1930).
Bircher, E.: Deutsche Ztschr. f. Chir. **182**: 229. 1923.
Bolaffio, Tedesco, Falta: (Cited by Falta.)
Bouchardat: 1851, (cited by Hellwig, 1930).
Büttner, G.: Bruns' Beiträge Zur Klin. Chir. **147**: 623. 129.
Cameron, A. T. and J. Carmichael: Am. J. Physiol. **58**: 1. 1921.
Collip, J. B. and E. P. Clarke: J. Biol. Chem. **67**: 679. 1926.
Csépai, K. and St. Pellâthy: Münch. Med. Wchnschr. **78**: p. 813. 1928.
Delaunay, H.: Biol. med. **20**: 289. 1930.
Eichler O. and R. Sanders: Klin. Wchnschr. **9**: 1618. 1930.
Eppinger, H.: Zur Pathologie u. Therapie des menschlichen Oedems. 1917. J. Springer, Berlin.
Falta, W.: Mohr-Staehelin's Handbuch d. Inn. Med. **4**: 1035. 1927.
Forschbach, J.: Arch. f. exper. Path. u. Pharmakol. **58**: 113. 1908.
Fraisseix, J.: Goitre exophthalmique et Tétanie, Thèse de Paris. 1900.
v. Frankl-Hochwart: Die Tetanie, II Aufl. 1907. Wien (cited by Falta).
Frank, E., R. Leiser, St. Weiss: Ztschr. f. klin. Med. **114**: 219. 1930.
v. Gebele: Bruns' Beiträge Zur Klin. Chir. **70**: 20. 1910.
Grafe u. Mark: Bericht über d. Internistkongress, Wiesbaden, 1929.
György, P.: Klin. Wchnschr. **9**: 102. 1930.
Hall, S. H.: Med. Press, **199**: 436. 1925.
Hellwig, A.: Klin. Wchnschr. **9**: 1913. 1930.
Herzfeld, E. u. J. Neuberger: Deutsche med. Wchnschr. **1**: p. 1384 (cited by McCullagh).
Hirschl, J.: Jahrb. f. Psych. u. Neurol. **20**: 406. 1901.
Wien. klin. Wchnschr. **17**: 608. 1904.
Holle and Weiss: Cited by Falta (1927).
Holmgren, I.: Basedow'sche Krankheit u. Längenwachstum. 1909. Diss. Stockholm.
Hunter, D.: Lancet **1**: 897; 947; 999. 1930.
Jakobi, J.: Wien. klin. Wchnschr. **17**: 768. 1904.
Ztschr. f. Nervenheilk. **32**: 1907.
Kahn and Falta: Cited by Falta.
Kay, H. D.: J. Biol. Chem. **89**: 235. 1930.
Klose, H.: Chirurgie der Thymusdrüse (Neue D. Chir.). 1912.
Chir. d. Basedowsche Khr. ibid. 1929.
Klose, H. und H. Vogt: Bruns' Beiträge zur klin Chir. **69**: 1. 1910.
Koch, W. F.: J. Biol. Chem. **12**: 313. 1912.
Koeppen, H.: Neurol. Centralbl. **11**: 219. 1892. (Cited by Aub, et al.)
Krizenecky, J. and J. Podhradsky: Arch. f. Entwcklngsmech. d. Organ. **112**: 577. 1927.
Kummer, R. H.: Rev. med. Suisse Romande, **37**: 439. 1917. (Cited by Aub, et al.)
Kunde, Margaret: Am. J. Physiol. **82**: 195. 1927.
Kurokawa, K.: Japan M. World, **5**: 241. 1925. (Cited by McCullagh.)
König, W.: Klin. Wchnschr. **8**: 634. 1929.
Lahey, F. H.: Surg. Gynec. & Obst. **42**: 508. 1926.
Latzko: Jahrb. f. Psychiat. u. Neurol. **20**: 401. 1901.
Leicher, H.: Deutsches Arch. f. klin. Med. **141**: 85. 1923.
Liebesny, P.: Wien. klin. Wchnschr. **37**: 494; 521. 1924.
Lublin, A.: Ztschr. f. klin. Med. **114**: 33. 1930.
Löwenthal: Handb. d. Inn. Sekretion (Hirsch) **1**: 5. 1930.
McCallum, W. B.: Brit. M. J. **2**: 1282. 1906.
McCarrison, R.: Lancet, **1**: 147; 219; 365. 1913.
McCullagh, P.: Arch. Int. Med. **42**: 546. 1928.
Michaud: Chirurg. **2**: 1105. 1930.
Minea and Radovici: Compt. rend. Soc. de biol. **72**: 840. 1912.
Montanari, A.: Riv. di clin. med. **29**: 760. 1928.
Morgenstern: Klin. Wchnschr. **9**: 1381. 1930.
Nitschke, A.: Ztschr. f. exper. Med. **65**: 637. 1929.
Klin. Wchnschr. **8**: 794. 1929. **8**: 1123 and **9**: 1192. 1930.
Palladines, A and L. Grilliches: Biochem. Ztschr. **146**: 458. 1924. (Cited by McCullagh.)
Parhon, C.: Compt. rend. Soc. de biol. **72**: 329. 1912.
Endocrinology, **7**: 311. 1923.
Parhon, C. et Cahane: Compt. rend. Soc. de biol. **103**: 191. 1930.
Paton, Noel: Quart. J. Exper. Physiol. **10**: 193. 1916.
Edinb. M. J. **31**: 541. 1924.
Pighini, G.: Riv. sper. freniatr. **44**: 409. (Cited by Hellwig.)
Plummer, W. A.: Proc. Staff Meetings of the Mayo Clinic. **3**: 119. (Cited by Hunter).
Rabinowitch, I. M.: J. Lab. & Clin. Med. **9**: 543. (Cited by McCullagh).

v. Recklinghausen: Festschr. f. Rud. Virchow, 1891. Reimer, Berlin.
Reiss, M., Winter, K. A., u. Halpern, N.: Endokrinologie. **5**: 230. 1929.
Répin, Ch.: Compt. rend. Soc. de biol. **71**: 225. 1911.
Salvesen, H. A.: J. Biol. Chem. **56**: 443. 1923.
Sattler, H., u. L. Borchardt: Ergebn. d. ges. Med. **15**: 223. 1930.
Schliephake, E.: Klin. Wchnschr. **8**: 2098. 1929.
Schneider, M., u. A. Nitschke: Klin. Wchnschr. **9**: 1489. 1930.
Schultze, Fr.: Berl. klin. Wchnschr. **34**: p. 177. 1897.
Sklover, A.: Ztschr. f. vergl. Physiol. **6**: 150. 1927. (Cited by Schneider und Nitschke).
Steinlechner: Wien. klin. Wchnschr. **9**: 5. 1896.
Stocker, H.: Deutsche Ztschr. f. Chir. **222**: 357. 1930.
Wein. klin. Wchnschr. **43**: 1116. 1930.
Tanabe, H.: Beitr. z path. Anat. u. z. allg. Path. **73**: 415. 1925.
Wade, P. A.: Am. J. M. Sc. **177**: 790. 1929.
Vassale, G., and F. Generali: Arch. ital. de biol. **33**: 154. (Cited by McCullagh), ibid 1906. (Cited by Falta).
Watanabe, C. K.: J. Biol. Chem. **73**: 253. 1918.
Wilms: Zentralbl. f. Chir. **37**: 661. 1910.
Wyssmann, K.: Biochem. Ztschr. **216**: 66. 1929.

FURTHER STUDIES ON ERYTHROCYTE SEDIMENTATION TIME IN RELATION TO THE FUNCTION OF THE THYROID GLAND

E. P. TSCHERNOZATONSKAIA
State Institute of Experimental Endocrinology
MOSCOW

In a former communication (1), my observations on the different rates of the red cells sedimentation as depending upon the functional state of the thyroid gland were given. The quickening of this process in the case of hyperthyreosis and its diminished velocity in that of hypothyreosis was noted, and was confirmed by experimental research on 146 sheep and eight rabbits, and by clinical observations of 27 subjects. The further problem was to elucidate whether one can attain a standardization of the thyreocrin and the antithyreocrin, taking as a basis the changes in the reaction of the erythrocytes sedimentation, and to find out what these changes are in different diseases of the thyroid gland.

EXPERIMENTAL STUDIES

Twenty-five guinea pigs were used for the standardization experiments—10 females and 15 males, weighing from 400 to 800 grams. Blood was taken from the vein of the ear, and observations were made according to the method of Pantschenkoff, by determining the height, in millimeters, of the sedimentation column in the course of an hour. With normal guinea pigs the reaction varied from 2.5 to 6 mm. per hour. The reaction was studied in all the animals in the morning from 9 to 12. Ten guinea pigs were given thyreocrin,* eleven antithyreocrin,* and four were control animals.

The observations with the animals went on during five weeks. The sedimentation time was first studied in normal animals, and then, after the introduction of the preparations, also in the intervals between their introduction.

The guinea pigs showed themselves more resistant as regards thyreocrin, than the sheep, spoken of in a former work. On an average, daily administration of 0.03 gr. of dry thyreocrin per kilogram of weight was sufficient for sheep, whilst the guinea pigs could tolerate a dose of 0.3 gr. per kilogram, i.e., a ten times greater dose. A further increase in the dose of the preparation made the sheep, as well as the guinea pigs, grow very thin and led to tachycardia, accelerated breathing and, in two cases, caused the death of guinea pigs from exhaustion due to thyreotoxicosis.

Dry thyreocrin was fed to the guinea pigs in tablets of 0.1-0.2 gr. in 24 hours, rolled into little pieces of bread or dough, as otherwise the guinea

*Thyreocrin and antithyreocrin mean the same things as thyreoidine and antithyreoidine.

pigs would not swallow them. In the intervals between the first and the repeated introduction of dry thyreocrin, during the period of the normal sedimentation of the erythrocytes, one tablet of thyroxin of Kahlbaum, containing 0.001 mgm. of pure thyroxin, was given daily for several days. This preparation did not have the slightest influence on the sedimentation time, although more iodine was used than with the dry thyreocrin (thyroxin—4.05 mgm. of iodine in 24 hours and 0.3 mgm. with thyreocrin).

Our experiments with guinea pigs showed that the erythrocyte sedimentation was quickened by an increase in the dose of thyreocrin, but a repeated introduction of thyreocrin called forth a weaker acceleration. With the first introduction of thyreocrin the sedimentation velocity increased from 3.3 mm. to 8.7 mm. and with the repeated experiment from 3.7 mm. to 7 mm. per hour.

After a fortnight's rest, the same guinea pigs were given liquid thyreocrin, obtained by the method of Kravkoff, from isolated thyroid gland of sheep, and preserved by means of chloroaethon. A subcutaneous injection of 1-2.5 cc. of this preparation was made daily for five days and gave almost as great an acceleration of the sedimentation time as did the dry thyreocrin: the reaction rose from 3.5 mm. to 7 mm. per hour. The chemical analysis of the Kravkoff preparation of thyreocrin did not show in it either iodine or protein. Simultaneously with these experiments four of the control guinea pigs, having received a subcutaneous injection of Ringer-Locke solution, preserved in chloroaethon, did not present any acceleration of the sedimentation time.

Two weeks after the termination of the observations with the thyreocrin of Kravkoff three guinea pigs were injected daily for five days with 1-2 cc. of liquid thyreocrin, prepared by Steppuhn through hydrolysis. Of the three guinea pigs, only one showed an insignificant acceleration of the sedimentation time; in both the others the reaction remained all the time within the limits of the norm.

Each cc. of the Steppuhn thyreocrin is equivalent to 0.1 gr. of dry thyreocrin, containing correspondingly 0.002 gr. of iodine. In spite of this, it did not quicken the reaction. It is possible that the variations of the sedimentation time are due not to thyroxin, but to some other substance. These data confirm the supposition of Shervinsky (2) and Zondek (3) as to the polyvalency of the thyroid gland hormone and also the opinion of Lucien, Parisot and Richard (4), who attribute to the thyroid gland a function of secretion of a plurality of active agencies.

Antithyreocrin was given to 11 guinea pigs. One of them died accidentally of pneumonia before the end of the experiment. At first, 1 cc. of liquid antithyreocrin was given subcutaneously to several guinea pigs, and, as a control, some normal sheep serum, also preserved in chloroform, like antithyreocrin, was injected into other guinea pigs. In both cases the sedimentation velocity was accelerated.

It is probable that, in this last case, the antithyreocrin, injected subcutaneously in a large dose, acted as a protein, not being free from it. A similar acceleration of the reaction, following the introduction of a normal serum, has also been pointed out by Löhr (5).

The introduction per os of liquid and dry antithyreocrin produced a noticeable retardation of the sedimentation time. During the periods, when the feeding with these preparations did not take place, the reaction became normal. On the other hand, it was seen that though an increase of the dose of antithyreocrin furthered the slowing of the reaction, yet this retardation did not surpass 1 mgm. per hour, i.e., it presented a variation of the reaction within normal limits. On the other hand, with the thyreocrin, an increase of the dose produced an augmentation of the sedimentation velocity equal to 2-3 mm. per hour. Consequently, the introduction of thyreocrin calls forth sharper changes in the reaction than that of the antagonistically acting antithyreocrin.

After an interval of two weeks, the same ten guinea pigs were given a dry thyreocrin prepared by another method (out of clots of blood of thyreodectomized sheep, clots preserved several months in alcohol). After receiving this preparation for five or six days in the proportion of 2-3 mgm. daily, the animals did not show the slightest change of the sedimentation time, probably because of a lack of an active element in this preparation. A loss in weight was noted, whereas the introduction of antithyreocrin led, in some cases, to a considerable increase in weight, whilst in other cases the latter remained unchanged.

CLINICAL STUDIES

In a former work the results of the researches upon the red cell sedimentation time in 27 patients suffering from diseases of the thyroid gland were given. In the course of one year this material increased to 646 subjects, of which 104 were studied in Moscow and 542 in the Mariyskaja province.

The blood for the research was taken from the soft part of the finger. The determination of the reaction was made according to the Pantchenkoff method, in which the normal sedimentation time in man varies from 5 to 8 mm. per hour.

There were 97 subjects presenting hyperthyreosis, who showed an acceleration of the sedimentation velocity from 10 to 45 mm. per hour, or an average of 20 mm. per hour. The quickening of the reaction went hand in hand with the seriousness of the case. There were 27 patients with hypothyreosis who showed a decrease of the sedimentation velocity from one to four millimeters per hour, or averaged 3.2 mm. per hour. Lastly, there were 528 subjects, afflicted with endemic goiter, accompanied by different forms of dysthyreosis, out of which 12 presented a normal reaction, 29 a reduced one, and 487 an accelerated one. In the last group, 50 subjects suffered, at the same time, from different accompanying affections; tuberculosis of the lungs, bronchitis, vitium cordis, arthritis or furunculosis,

which led possibly to an alteration in the reaction. Besides, several of the women affected with goiters suffered from gynecological disturbances, whose exact diagnosis it was not possible to make. The other subjects with dysthyreosis, as well as those with hyperthyreosis or, hypothyreosis, did not suffer from any accompanying disease.

As to the symptoms of hypothyreosis, with which the accelerated rates of sedimentation velocity mostly coincided, a heightened sweating thermophobia and irritability must be mentioned. These were often observed not only in the cases of Basedow dysthyreosis, but also in those of mixed forms of dysthyreosis, and sometimes even in the myxedematous ones.

The majority of the patients suffering from hyperthyreosis presented an acceleration of the sedimentation velocity from 15 to 20 mm. per hour, whilst those afflicted with hypothyreosis showed, for the most part, a reduction of the rate up to 4 mm. per hour. Therefore, the deviation from the norm is, in hypothyreosis, considerably less marked than in hyperthyreosis.

The majority of those suffering from dysthyreosis showed a velocity of erythrocite sedimentation equal to 10-20 mm. per hour. The last ten patients, who presented velocity rates from 50 to 70 mm. per hour, were suffering not only from dysthyreosis, but also from an active form of tuberculosis of the lungs, which led to such rapid rates. Besides these cases I had nine more with dysthyreosis and tuberculosis of the lungs in a weaker degree, and all presented accelerated sedimentation rates. However, Borok, Zoubin and Mordvinkina (6) found that hyperthyreosis combined with tuberculosis of the lungs showed a slower velocity, and the combination of hypothyreosis with tuberculosis quickened the sedimentation time. Probably these facts depended rather upon the degree of development of the tuberculosis than upon the thyroid gland function being disturbed.

About 200 cases were observed in order to study the relationship of the erythrocyte sedimentation rates to the progress of different thyroid gland diseases. In all these cases it was found that repeated observations of the sedimentation time variation were more useful than isolated ones. As in tuberculosis, so in thyroid gland diseases, this variation can be used for prognosis and therapeutics. Its increased deviation from the normal always pointed to a progress in the malady, and its approaching the normal figures (readings) showed an amelioration in the patient's health. In the course of a treatment with thyreocrin, the continued investigation of the sedimentation time were of the greatest help, in the sense that they made it possible to choose the right dose of thyreocrin for every individual patient, thus preventing the possibility of a thyrotoxicosis due to excessive doses being given.

In the course of dysthyreosis, frequently in the case of one and the same subject, the symptoms of hyperthyreosis were periodically succeeded by those of hypothyreosis, and then the erythrocyte sedimentation rate, before any other symptoms took an inverted direction pointing to a reversal in the morbid process.

SUMMARY AND CONCLUSIONS

1. The degree of variation in the sedimentation velocity after the introduction of different thyroid gland preparations and of antithyreocrin into guinea pigs can furnish an approximate evaluation of the comparative power of the above mentioned organotherapeutic medicaments employed.

2. These preparations cannot be standardized according to the variations of the sedimentation time, owing to the instability of this reaction in its relation to different external and internal factors.

3. The investigation of 645 human cases has shown that pure forms of hyperthyreosis are always accompanied by an acceleration of the reaction, and those of hypothyreosis by a decrease of velocity rates. In the cases of Basedow's disease and mixed dysthyreosis, the rates are mostly rapid, and in the myxedematous forms of dysthyreosis they are very often diminished.

4. Repeated investigations of the sedimentation time in the course of different thyroid gland diseases can be most useful for the prognosis and for the treatment of the malady, as a strong deviation from the normal action always indicates a progress in the morbid process, whilst its approaching the normal rate points to an amelioration in the patient's state.

In concluding, I beg to express my sincere thanks to Prof. Shervinsky for kindly proposing this theme and for his valuable help during my work, and also to Prof. O. A. Steppuhn and Dr. P. V. Botchkareff for their useful advice in the course of my researches.

REFERENCES

1. Tschernozatonskaia, E. P.: Ztschr. f. d. ges. exper. Med. **66**: 67, 1929; Klin. Wchnschr. **8**: 791. 1929.
2. Shervinsky, V. D.: Viestnik endokrinologii, Nr. 4. 1925.
3. Zondek, H.: Die Krankheiten der endokrinen Drüsen. Ein Lehrbuch für Studierende und Aerzte. 1923.
4. Lucien, M., J. Parisot and G. Richard: Traité d'endocrinologie. Paris, 1929. Doin et Cie.
5. Löhr: Ztschr. f. d. ges. exper. Med. **27**: 1. 1922.
6. Borok, M. R., I. M. Zoubin and V. I. Mordvinkina: Voprosy Tuberk. **6**: 16. 1928.

SOMNOLENCE ASSOCIATED WITH PITUITARY CACHEXIA

CASE REPORT OF A PATIENT WHO RESPONDED TO PITUITARY TREATMENT

BERNARD E. McGOVERN, M.D., B.Sc.
NEW YORK

The following case report concerns a female patient, who suffered from an advanced stage of pituitary cachexia, and in whom uncontrollable somnolence was a prominent feature. Previous to treatment, the severity of her condition approached that of Simmond's disease (acquired total insufficiency of the anterior lobe of the pituitary gland). A gratifying manifestation in her case was the definite and rapid manner in which both the cachexia and the somnolence responded to pituitary substitution treatment.

History: An unmarried nurse first came under observation May, 1931, when she was 23. She had spent most of her life in the state of Colorado.

Family History: The family history was not informative except that one brother, 26 years of age, had exhibited, three years previously, symptoms of anterior pituitary lobe failure (loss of weight, strength and libido). He had responded satisfactorily to pituitary substitution treatment.

Past History: During childrood the patient had suffered from mumps, whooping cough, pneumonia and chicken pox. During her juvenile period she grew very rapidly and was inclined to overweight. She had no great difficulty in keeping up with her school classes or during her nurse's training period but she had always tired easily.

Menstrual History: Her menses began at the age of 13. Occasionally they had been a few days late in starting, but she had never missed a whole month. Her periods usually lasted three days, and she generally had to use four napkins a day. For several days previous to the beginning of each period she had suffered moderately from backache and abdominal cramps. She stated that for about one year previous to this examination her menses had been gradually diminishing in amount but not in duration.

Present Complaint: The chief complaints for which the patient sought advice were somnolence, loss of weight, weakness, extreme fatigability, loss of memory, abdominal pain, mental depression, irritability, loss of ambition and dryness and loss of hair. The attacks of sleepiness occurred several times a day; she would go to sleep anywhere as, sitting at the table, or riding in a car. The individual attacks varied in duration from a few minutes to about a half hour; during this period she could be awakened with difficulty, or not at all. She sometimes was troubled with insomnia at night but the attacks of somnolence were always diurnal.

Eight months previous to this observation, the tendency towards somnolence, fatigue and loss of memory had become so marked that she was forced to give up her work as a nurse. During the interval her appetite had been poor and her weight had dropped from 122 to 109 pounds.

At the age of 11, she had experienced a similar attack but the symptoms then were much less severe and the duration was shorter. At this time the somnolence amounted to only transient periods of drowsiness.

During youth her teeth began to crumble, and this tendency had continued up to the time the patient sought advice.

She complained of having had frequent attacks of acute tonsilitis and acute rhinitis. Accompanying the attacks of rhinitis, and to a lesser extent between attacks, she had suffered headaches, which included the occipital region, the region over the right eye, and the right side of the head. She also complained of "waves of hot flashes", cardiac palpitation, diffuse abdominal pain, morning nausea and vomiting, constipation, and dizziness.

About eight months previous to the observation herewith reported, a physician had found that the sugar content of her blood was low; he advised her to eat more carbohydrate. After an exhaustive survey of her gastro-intestinal tract, he found no evidence of organic disease. He believed her symptom complex suggested Addison's disease and he advised her to try ephedrine sulphate, for both the weakness and the somnolence. The ephedrine seemed to increase her tendency to nausea and she abandoned its use.

Physical Examination made on May 18th, 1931, showed the patient to be poorly nourished, of shriveled, aged appearance; her skin was dry. There was no anemia apparent from inspection of her skin, mucous membranes or finger nails. Her height was 5 feet, 4 inches, and her weight was 109 pounds, clothed. Her scalp was very dry, and the hair was brittle and sparse over the scalp; it was especially sparse over the vertex region. Her face was triangular-oval in shape and short. There was a slight increase of facial hair and a slight accentuation of that on the upper lip.

There was no edema of the eye-lids or face. No lid lag or exophthalmos could be detected. The eyes converged normally on looking at close objects; they also followed a point in all directions, reacted promptly and within wide limits to light and accommodation. There was neither contraction of the visual field nor scotoma elicitable by the rough clinical method of a moving object. The patient was able to frown, close her eyes tightly, raise the eyebrows and retract the angles of her mouth. No Chvostek sign could be elicited.

Her teeth were small, the upper lateral incisors especially so; she had many artificial and gold-filled teeth. The gingival margins were moderately retracted. The mucous membranes were pink. The tonsils were buried, ragged and cryptic, and the pillars were injected. The palate rose normally when the patient said, "ah."

The nasal septum was deflected to the right, pressing against the upper turbinates; the mucous membranes were somewhat swollen but there was no purulent secretion present.

The dorsae of the hands were slightly full, and the palms dry. There was no tremor in the extended fingers when the arms were fully outstretched. The deep arm reflexes were normally active and there was no ataxia when the patient attempted to touch the end of her nose with her finger with eyes shut. Trousseau's sign could not be elicited.

The cervical lymphatic glands on the right side were enlarged and tender. The thyroid gland was moderately enlarged, firm and somewhat nodular. The trachea was in the midline.

The patient could shrug her shoulders and turn her head from side to side without difficulty.

Some dilated superficial veins could be seen between the scapulae. The ribs stood at a slightly more obtuse angle than normal. No localized lagging of the chest could be detected. There was a slight amount of hyperresonance over the entire chest region. The excursion of the lungs at the base and apices was moderate as shown by percussion. There were no persistent adventitious sounds heard over the chest.

The heart dullness was within normal limits; the pulse rate 75; the rhythm was regular; there were no murmurs.

The systolic blood pressure was 110 mm. of mercury and the diastolic was 70 mm. No hardening of the palpable arteries was noted.

There was tenderness over the sigmoid region during pressure and the sigmoid colon could be palpated as a rope-like mass. There was good flexibility of the spine in all directions and there was no tenderness over that region.

There was no edema of the lower extremities. The knee jerks were active and equal; the Achilles tendon reflexes were present; there was no Romberg sign.

Laboratory Investigation (by Drs. P. Hilkowitz and A. Freshman):

Urine: The specific gravity was 1016; there was no sugar; the reaction was acid; a few pus cells per field were present; albumin was 5 mgm. per 100 cc.

Blood: The sugar content was 133 mgm. per 100 cc; the erythrocytes were 4,300,000 per cubic mm.; the hemoglobin by the Dare instrument was 88 per cent; the leucocyte count showed 4,000 white cells per cubic mm.; the percentages of the leucocytes present were: polymorphonuclear leucocytes, 51; lymphocytes, 46; large mononuclear leucocytes, 3. The patient was fasting when the count was made. The Wassermann reaction of the blood was negative.

Stool: There were no occult blood, no mucous, no parasites or ova present.

Basal Metabolism: The basal rate was minus twelve per cent.

Roentgen Ray Examination (by Dr. Arnold Minnig): There was noted slight clouding in the lower angles of the maxillary sinuses, suggesting the presence of a small amount of hyperplastic tissue. The chest showed a darkening throughout the entire lung fields, suggesting overaeration from a small degree of emphysema; also, the angles of the rib shadows were slightly more obtuse than normal.

Diagnosis: There was evidence of hypoactivity of the anterior lobe of the pituitary gland, with a small degree of secondary hypoactivity of the thyroid gland, ovaries, and possibly of the adrenal cortices; chronically infected tonsils; chronic hyperplastic sinusitis of a mild degree; and an early stage of emphysema.

Treatment and Progress: The treatment was begun by giving the patient 2 cc. subcutaneously of "Anterior Pituitary Liquid" (Armour) every other day. During the first week of treatment, the patient was also given one-half grain of desiccated thyroid daily; the thyroid medication was then discontinued. Along with the anterior pituitary liquid, "Ovarian Substance Soluble Extract" (P.D. and Co.) was given in a dosage of 2 cc. subcutaneously every other day. After one month the patient complained of excessive menstruation, and the Ovarian Substance was discontinued.

One month after starting treatment the patient had gained 6½ pounds; her appetite had improved; the headache had lessened; her hair was less dry; there was an appreciable improvement in the tendency toward somnolence; her energy was considerably greater. It might be mentioned here that the headache could be entirely relieved for varying periods of time by shrinking her turbinates with epinine, ephedrine, or cocaine, and by applying a ten per cent solution of cocaine to her sphenopalatine ganglia. Evidently, then, the headaches were due mainly to the nasal condition, but she insisted that the anterior pituitary liquid had also a significant effect in relieving the headaches.

After two months of treatment with the pituitary liquid, the attacks of somnolence had decreased and her energy and ambition had increased to such an extent that she began to make plans to take some post-graduate work. Also, she had taken up horseback riding. The gastrointestinal symptoms had disappeared and her weight was 118 pounds clothed.

During August, 1931, she had an attack of acute tonsilitis, complicated by cervical adenitis. After the subsidence of the attack, her tonsils were removed. This operation was followed by the disappearance of the adenitis, and by a general improvement.

During the early course of her treatment, the pituitary liquid was discontinued for a week on several occasions; a return of the somnolence followed. At such times thyroid substance in larger doses was tried in place of the pituitary substance, but it seemed to make the patient uncomfortable when the dosage was increased, and it did not control the attacks of somnolence to any great extent.

At the end of the third month of pituitary treatment, the patient was still improving. She had lost the shriveled appearance; her appetite was excellent: she no longer complained of sleepiness; her hair was less brittle; her weight had increased to 122 pounds clothed, and she said she felt better than she had for many years.

The effect of doing without pituitary liquid was again tried, and she was able to go for a week at a time without the treatment, without lapsing into somnolence.

DISCUSSION

It seems to be a well established fact that the basophilic cells of the anterior lobe of the pituitary gland are associated with the development and functioning of the gonads, thyroid, suprarenal cortices and parathyroid glands; and that the eosinophile cells of the anterior lobe stimulate general body development and muscular vigor.

The thyroid deficiency suffered by some of these patients having pituitary cachexia is probably often due to lack of stimulation from the anterior lobe; the same statement may be made of the gonads, adrenal cortices

and probably of the parathyroids. It therefore seems logical to lay special emphasis upon the pituitary gland in the treatment of this condition, even though several other glands are involved. However, substitution or stimulatory treatment for the glands secondarily involved would not be out of place, and substitution treatment would be especially indicated if these glands were unable to respond to stimulation, or if potent pituitary preparations could not be secured.*

"Pituitary hibernation" is a condition closely related to pituitary cachexia, but there is this difference: In "pituitary hibernation" the thyroid may possibly be more extensively involved, but the main difference lies in the fact that there is obesity instead of loss of weight. The obesity is supposed to be at least partly due to failure of the neurohypophyseal mechanism (posterior lobe, pars tuberalis, infundibulum, and hypothalamus complex). The details of this neuro-glandular complex and its association with the development of obesity have not yet been thoroughly established.

Engelbach has for many years insisted that patients suffering from "pituitary hibernation" are also suffering from deficiency of the thyroid gland; he early pointed out that better results can be obtained by combined thyroid and pituitary therapy than when either is given alone.

The conditions that will impair the pituitary gland or the contiguous and probably interrelated nervous structures are numerous; congenital or hereditary weakness of the structures must be considered. Of the active causes, it seems logical to place infections among the more prominent. In the case of the patient just reported, the chronic tonsillar infection may have played some part as an exciting cause, since after the tonsils were removed it required less of the pituitary liquid to keep her free from the attacks of drowsiness than prior to the operation.

SUMMARY

The case of a female patient, aged 23, who was suffering from pituitary cachexia is reported. Her chief complaints were: a severe grade of somnolence, loss of appetite, loss of weight, abdominal pain, constipation, diminution of menses, extreme exhaustion, mental depression, impairment of memory, and dryness and loss of hair.

She was given anterior lobe pituitary extract hypodermatically for about four months, and in response to the treatment gained 13 pounds, became practically free from somnolence and other mental symptoms, experienced restoration of normal menses, and regained her strength and energy.

During the course of treatment the pituitary liquid was withheld on several occasions and she promptly lapsed into her former state, but each time quickly responded again to the resumption of the treatment.

*It is realized that not a few of the proprietary endocrine preparations are of doubtful potency, but as the more scientifically prepared extracts of the pituitary gland, such as those of Herbert Evans were not obtainable, the proprietary preparations were tried in their stead.

During the third month of observation and treatment chronically infected tonsils were removed, after which there was some general improvement, and the patient was able to withstand deprivation of the pituitary treatment, without symptoms, for longer periods than before. It appears that chronic infection was impairing or aiding in the impairment of an inherited or congenital weakness of the anterior lobe of the pituitary.

PERIODIC PARALYSIS OCCURRING IN THE COURSE OF EXOPHTHALMIC GOITER*

JACOB M. MORA, M.D.
Assistant Professor of Surgery, University of Illinois College of Medicine
CHICAGO

Dunlap and Kepler (1) recently reported four patients with exophthalmic goiter who were subject to attacks clinically identical with those seen in the syndrome known as "familial periodic paralysis." This condition was said to be characterized by hereditary transmission, periodicity, confinement to the motor portion of the nervous system, electrical changes, and by the apparent good health of the patient in the interval. During a typical attack the patient presents total or partial flaccid paralysis of the extremities and at times of the muscles of the trunk and neck. Paralysis begins in the proximal portion of the limb, progresses distally, and disappears gradually in reverse order to that in which it came on. Nothing is known of the cause of this condition. Charcot (2) is credited with being the first to describe the occurrence of paraparesis and paraplegia in the course of Basedow's disease. Möbius (3), too, was familiar with the symptom-complex, and Oppenheim (4) reports the statement made to him by Saenger and Edenger that they had noted the occurrence of periodic paralysis in association with exophthalmic goiter. Shinosaki (5) reported a study of 24 cases, in seven of which a diagnosis of Basedow's disease was made. Rosenfeld (6), many years ago, described a case of Basedow's disease with paroxysmal acute ascending paralysis of the Landry type and Hector Mackenzie (7), in his "Clinical Lectures on Graves' Disease" in 1890, includes a description of the phenomenon of "giving way of the legs" occurring in this disease, which in many ways was similar to the syndrome under discussion.

The four patients described by Dunlap and Kepler were all males, varying in age from 29 to 35 years. In all four instances the attacks of paralysis followed the development of the thyrotoxicosis. Two of these patients experienced complete relief following thyroidectomy. The third patient was relieved by roentgen therapy and iodine. The fourth patient, who was not relieved of the recurring attacks of paralysis, was believed to be suffering from a recurrence of his thyrotoxicosis.

The report by Dunlap and Kepler prompted us to record a case of similar nature:

H. P., male, 33 years old, was operated upon in August, 1922, for high grade thyrotoxicosis of two years' duration. Radical thyroidectomy was performed. The patient was not seen again until January, 1930, when he returned with what appeared to be a definite recurrence of all of his former thyrotoxic symptoms, which he stated began in the spring of 1929. Satisfactory study was again delayed until January, 1932, when he described a most interesting group of symp-

*From the surgical service of Dr. H. M. Richter.

toms, of two years' duration. On numerous occasions while walking, he would suddenly experience (without apparent cause) a feeling of great weakness and "drawing" in the thighs, extending to the legs and feet, followed by collapse. He felt "paralyzed," and would have to be carried to a chair or bed. These attacks would last from thirty minutes to an hour or more. On other occasions a similar train of symptoms occurred when he stepped from an automobile. Several attacks were described in which the patient, while in bed, attempted to arise but found himself unable to do so for about one half hour—after considerable effort he had to "muscle himself up." He was very definite in his statement regarding the feeling of "weakness and numbness" which began in the thigh and progressed distally.

It is particularly interesting to note that this patient stated that the attacks of so-called paralysis always occurred after taking compound solution of iodine (which he took intermittently of his own accord.) He is now being prepared for operation.

SUMMARY

A case of exophthalmic goiter (recurrent) is described presenting symptoms similar to those described in so-called "periodic paralysis." This is the fifth case of its kind described in the English and American literature, four cases having been previously reported by Dunlap and Kepler.

REFERENCES

1. Dunlap, H. F. and E. J. Kepler. A syndrome resembling familial periodic paralysis occurring in the course of exophthalmic goiter, Endocrinology, **15**: 541. 1931.
2. Charcot, J. M.: Quoted by Oppenheim.
3. Möbius, P. J.: In Nothnagel, H.: Spezielle Pathologic und Therapie, **22**: 41. 1909. Alfred Hölder, Wien.
4. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, **II**: 2182. 1923. S. Karger, Berlin.
5. Shinosaki, T.: Klinische Studien über die periodische Extremitatenlähmung, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**: 564. 1925-1926.
6. Rosenfeld M.: Akute aufsteigende Lähmung bei Morbus Basedow, Berl. klin. Wchnschr. **39**: 538. 1902.
7. Mackenzie, Hector: Clinical lectures on Graves' disease, Lancet, **II**: 545. 1890.

A CASE OF MYXEDEMA WITH ASCITES AND ATONY OF THE URINARY BLADDER

WILLIAM EVANS
Medical Clinic, Peter Bent Brigham Hospital
BOSTON

This case was considered worthy of description inasmuch as a perusal of the literature reveals no record of the association of atonic bladder with myxedema and because a determination was made of the protein content of the ascitic fluid of which there is also no record in the literature. Disturbance in the function of nerve and muscle is not uncommon in myxedema. Most of the standard monographs (1-7) speak of the frequency of constipation, and this is generally attributed to atony of the bowel musculature (1, 3, 7). The dilatation of the heart occasionally observed has been ascribed to atony of cardiac muscle (8). A slowing (34) of tendon reflexes is described together with loss of acuity in hearing, sight and taste, as well as sexual impotence (3, 7), but so far as I know no one has described a disturbance of the musculature of the urinary bladder or its innervation. According to Falta (1) there is a definitely decreased irritability of the entire vegetative nervous system. In particular v. Cyon found that the electrical excitability of the vagus nerve was diminished in thyroidectomized dogs. Also as evidence of diminished excitability of sympathetic nerves is the failure of adrenalin to produce glycosuria in thyroidectomized animals and in myxedematous patients. Likewise the pressor effect and hyperglobulia produced by adrenalin are much diminished or absent. Eppinger is quoted as saying that the myotic effect of pilocarpin is much less and Asher to the effect that the mydriatic action of atropin is much prolonged in thyroidectomized dogs. Falta found a prolonged effect of homatropin on the eyes of human myxedematous subjects. This, together with other evidence, indicates that in myxoedema there is diminished excitability and a greater susceptibility to paralysis of the autonomic system. Eppinger believes there is a diffuse neuritis (3). Indeed it is surprising that there are not more widespread disturbances of autonomic function in the myxedematous patient. In this case the distended bladder was discovered quite by accident. It is not impossible that the condition is relatively common and that a residual urine would in part explain the low kidney function (dye excretion) (3, 9), and diminished urinary output which is described frequently.

The occurrence of free fluid within the body is not generally associated with myxedema, but a very few cases have been reported in which the fluid apparently was due to the thyroid state alone and not secondary to any cardiac or renal disease (10, 11). The chemistry of the fluid in this case and possibilities as to its origin will be discussed later.

CASE HISTORY

Mrs. M. B., 49, Med. No. 40415, entered the hospital January 30, 1932, complaining chiefly of swelling of the abdomen and difficulty in breathing for eight months. The family history was remarkable only in that two of the paternal relatives had suffered from rheumatism and that one sister had died of epilepsy. The patient herself had been married thirty years and was the mother of four healthy children (ages 30-22).

In her past history it was noted that she had completed the ninth grade in school at 14, although she had always been considered very slow in her reactions and thinking. There had been no serious illnesses with the possible exception of three attacks of "rheumatism," the last one being thirty years ago. In none of these attacks does she recall that her joints were reddened or swollen. The menopause had occurred uneventfully 7-8 years previously.

The present illness apparently began insidiously about 8-9 years ago, when she went to her doctor complaining of a rectal fissure and of epigastric distress associated with indigestion. At that time he noted her dry skin, made a diagnosis of hypothyroidism and prescribed thyroid tablets. She had attained then her maximum weight of 205 pounds. Under thyroid medication, which she took faithfully for four years, she lost considerably in weight and gained in a sense of general well being. During the following four years she took thyroid only when she was feeling heavy, slow and dyspnoeic, and then with striking relief of these symptoms. She had taken no thyroid for about a year previous to admission. The following may be said for symptoms referable to the systems:

Skin: Dryness of the skin, which had been noted 8-9 years previously, had become particularly marked with scaling during the past 4 years, since which time her hair had been slowly falling out. She had been aware of swelling of the legs for a year or more.

Eyes: Except for increasing presbyopia there had been no appreciable change in vision.

Ears: For nine months she had experienced some ringing and tinnitus occasionally but not to any disturbing degree.

Teeth: All were removed 3 years ago because of pyorrhea and caries.

Cardio-respiratory: For 8-10 years she had had some dyspnea on exertion, and during the past year there had been increasing orthopnea so that she did not lie down to sleep at night. More recently she had developed a slight cough productive of small amounts of white frothy sputum. There had been no chest pain or palpitation and no chills or fever.

Gastro-intestinal: For many years she had complained of some gas on the stomach and occasional attacks of "indigestion." She said she had always been constipated and was in the habit of taking a wide variety of cathartics. She had noted that a prolonged period of obstipation would be followed occasionally by diarrhea lasting 2-3 days. For 8 months there had been gradually increasing swelling of the abdomen.

Genito-urinary: There had been burning on urination for a number of months together with increasing difficulty in starting the flow of urine. There was a frequent desire to urinate but an inability to do so to complete satisfaction. There had recently been nocturia up to 3 or 4 times.

For about two years she had led a more and more restricted existence, while for a number of months she had not ventured from her home. She was sensitive to cold particularly in the winter time and was very fond of sitting in a chair close to the grate fire reading and sewing all day. Her mentality was not in the least dulled, and her daughters testified that she was at all times keenly aware of family affairs and had a lively sense of humor although her outward appearance seemed much to the contrary.

Physical Examination: On admission she presented a striking and textbook picture of far advanced myxedema so that the nurse made the diagnosis at one glance. She was sitting propped up in bed and experiencing some difficulty in respiration. The skin was very dry with fine white scales especially on the scalp and arms. It was everywhere tense but particularly in the lower portions of the legs, where there was slight pitting edema, although not so much as the degree of swelling would indicate. Over the cheeks the color of the skin was a reddish yellow while over the legs it was a dusky red; elsewhere it was pale and pasty. In the dependent portion of the abdomen the skin was very thick and indurated the pores being so prominent as to give a typical pig-skin appearance. Thick pads of subcutaneous tissue were prominent about the eyes, cheeks, neck,

supraclavicular fossae and dorsal surfaces of the hands and feet. The hair was gray, very dry, and fine, quite sparse on the scalp—particularly in the temporal regions—and almost absent in the axillae. The eyes were almost closed by the swelling of the lids. Otherwise the examination of the eyes including the eye grounds was negative. A watch tick could be heard only with the watch pressed closely to both ears. The tongue was very large and together with a large uvula obstructed all view of the pharynx. Speech, evidently as a result of this, was very slow, thick and labored. The difficulty seemed definitely more a mechanical than a psychic one. The upper lip was curiously everted and in advance of the lower one. Because of the thick masses of subcutaneous tissue palpation of the neck was very unsatisfactory, and likewise little could be learned from the ordinary physical examination of the heart and lungs. The diaphragm seemed elevated, and there were a few crackling rales to be heard at the left base posteriorly on deep inspiration.

The heart sounds were not remarkable and there was a blowing systolic murmur localized to the pulmonic area. The blood pressure was 120/70 and maintained itself at this level with minor fluctuations during her stay on the ward. The pulse for the most part was between 70 and 80, and the temperature curve normal. The abdomen was enormously distended and the wall tense like a drum, with a small, easily reducible, umbilical hernia. Percussion at the vertex gave a tympanitic note while in the flanks there was well marked shifting dulness. The tendon reflexes in the arms and legs were considered equally and normally active on the two sides. The pelvic examination showed some relaxation with a moderate rectocele. The vaginal mucosa was redundant, and there were two small external hemorrhoids.

The impression was one of far advanced myxedema with an abdomen distended by gas and fluid. The immediate treatment was directed toward reducing the abdominal mass, obviously a source of considerable distress. Cathartics, enemas, turpentine stupes and rectal tubes were employed without success. The urinary bladder was catheterized and 375 cc. of fluid obtained. On the following day there was no improvement, and if anything, the patient's distress had increased. It was, therefore, decided to perform abdominal paracentesis. This was done in the usual manner, the trocar being introduced in the midline about 1/3 of the distance between the symphysis pubis and the umbilicus. A slightly blood tinged, amber colored, fluid was obtained without difficulty. It had the appearance of urine and a very suggestive odor. The chemistry of the fluid established its identity with urine.

Amount—2500 cc.
Specific Gravity—1.018
Cells—5400 red blood cells/cu. mm. No white blood cells.
Urea+NH_3—210 mgm. N/100 cc.
Non-Protein Nitrogen—483 mgm./100 cc.
Creatinine—54 mgm./100 cc.
Cl—290 mgm./100 cc.
Uric Acid—28.2 mgm./100 cc.
Total Protein—0.42 gm./100 cc.
Albumin—0.21 gm./100 cc.
Globulin—0.21 gm./100 cc.

Fortunately no untoward symptoms developed from this operation. Subsequently there was some spontaneous urination, but in addition catheterizations once or twice daily were employed and on such occasions 400-1500 cc. would slowly dribble from the catheter. The urine on admission was described as clear, amber, acid, of specific gravity 1.010, without either albumin or sugar, but containing a rare leucocyte and hyaline cast and no red blood cells. Subsequent specimens contained a moderate amount of albumin and a number of leucocytes although after 18 days the albumin had decreased to the slightest possible trace and finally disappeared entirely. A low grade cystitis persisted throughout. On the fifteenth day and for two days following the urine was grossly bloody. This was attributed to urotropin and disappeared when urotropin was discontinued. On the nineteenth day cystoscopy was performed by Dr. Quinby. "Extensive atony" was found "with here and there areas of cystitis." The tone was said to be fair with the bladder containing above 400-500 cc. Below this amount there was no voluntary control. A cystogram with 70 cc. showed a "bladder smooth in outline, but with a funnel shaped neck similar to that seen in spinal bladders." Irregular dense shadows were noted in the kidney areas suggesting calculi. Under thyroid therapy the tone of the bladder gradually improved, so that finally

no residual was present after urination. A negative Wassermann reaction and no clinical evidence of a neurological lesion together with the improvement noted under thyroid medication would seem to establish well enough thyroid insufficiency as the sole cause of bladder atony in this instance.

Following the suprapubic bladder drainage a week passed without any signs of improvement. The abdomen remained distended, and there was still dulness in the flanks which shifted on movement. Dyspnea was, if anything, increasing and the patient was very uncomfortable. In view of this it was decided to attempt once more abdominal paracentesis, this time making sure that the bladder was properly drained through a longer catheter and under more careful supervision. On the eighth day, therefore, a trocar was again inserted into the abdominal wall at approximately the same place as before. A hazy greenish yellow fluid was withdrawn having the following characteristics:

Amount—2000 cc.
Specific gravity—1.020
Cells—77 mononuclear white blood cells; 335 red blood cells/cu. mm.
Total Protein—5.1 gm./100 cc.
Albumin—2.9 gm./100 cc.
Globulin—2.2 gm./100 cc.
Non-Protein Nitrogen—23 mgm./100 cc.

Following this procedure improvement began in a rapid and progressive fashion.

Teleo-roentgenograms were made of the patient at regular intervals as indicated on the chart in which the ratio of the transverse diameter of the heart to the chest is plotted. In addition to well marked enlargement of the cardiac shadow the first film, made on the fifth day, showed a small amount of fluid at the left costo-phrenic angle. On the eighteenth day when it was decided to remove a small portion of this fluid for chemical study none could be obtained.

Other laboratory findings were as follows:

1st day	Hb. 80%	R. B. C. 3,400,000	W. B. C. 6,700
6th day	B. U. N. 14	P. S. P.—24%	
8th day	Hb. 82%	R. B. C. 3,520,000	W. B. C. 11,000
13th day	Hematocrit Reading		
	Cells 36%	Plasma 64%	R. B. C. 4,110,000
	I. C. V. 8.7×10^{-11} cc.		
	Blood Iron	40.3 mgm./100 cc.	
16th day	Hb. 85%	R. B. C. 4,350,000	
18th day	B. U. N. 13	N. P. N. 37	
	T. P.—7.6	Alb. 4.6	
	Glob. 3.0		
21st day	Blood Amino Acid	3.82 mgm./100 cc.	
22nd day	Hb. 76%	R. B. C. 4,310,000	W. B. C. 14,200
26th day	Gastric Analysis	(50 cc. 8% Alcohol by Mouth and .5 mgm. Histamine Subcutaneously)	

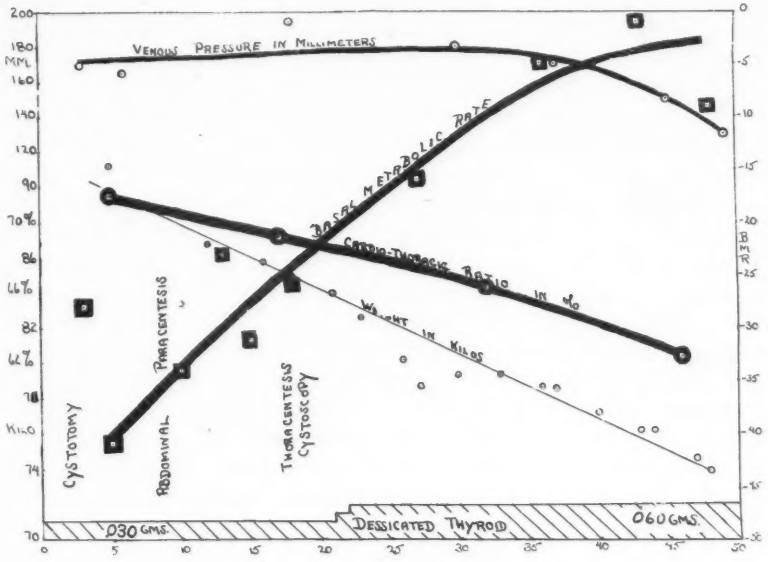
	Free Acid	Total Acid
Fasting	8	19
30 min.	49	59
60 min.	56	68
120 min.	16	28

30 th day	W. B. C. 9,000
37th day	W. B. C. 7,650
44th day	W. B. C. 9,150

45th day	R. B. C. 4,130,000		
49th day	T. P. 7.1	Alb. 4.0	Glob. 3.1
	N. P. N. 19		
51st day	Hb. 85%	R. B. C. 3,890,000	

Hb.—hemoglobin by Sahli, R. B. C.—red blood cells per cu. mm., W. B. C. —white blood cells per cu. mm., B. U. N.—blood urea nitrogen in mgm./100 cc., P. S. P.—phenolsulphonephthalein percentage of excretion of 1 mgm. injected intramuscularly in 130 min., I. C. V.—individual volume of average red blood cell, N. P. N.—non-protein nitrogen of blood in mgm./100 cc., T. P., Alb., Glob. —total protein, albumin, globulin of blood serum in gms./100 cc. All determinations of blood chemistry made on fasting blood.

For treatment the patient received a desiccated thyroid preparation beginning with 0.015 gm. twice a day on the fourth day and increasing to 0.030 gm. twice a day as indicated on the chart. In addition digitalis folia was given 0.1 gm. twice a day beginning on the seventh day and amounting to a total of 9.2 gm. in 46 days. Two Blaud's pills were given three times a day beginning on the second day. A soft solid obesity diet containing approximately 1200 calories was employed. The fluid intake was maintained at an average of 1200 cc. daily for the first 29 days and then increased to about 2000 cc. daily.



DISCUSSION

Fournier (10) described 5 cases of ascites associated with myxedema, two of them with hydrothorax, in which the fluid was removed by thyroid feeding. He quotes Nothnagel concerning a similar case successfully treated with thyroid. Unfortunately no basal metabolism studies were carried out, although the diagnosis seemed to be established clinically. Marsh (11) describes one case in which 3 gallons of fluid were removed by abdominal paracentesis, following which the fluid gradually returned, finally to disappear under thyroid feeding. One of Fournier's cases had albuminuria, which disappeared following treatment. In none of these cases was there said to be any evidence of cardiac or renal disturbance. Fournier definitely states that the heart was normal in all of his cases, although there is no record of any radiographic studies. Davidson (12) has described 6 cases of so-called "thyroid nephrosis." The descriptions of his cases are too brief to make this diagnosis entirely convincing, however, especially in view of the fact that we know albuminuria occasionally occurs in simple myxedema, and that it is rather the rule for there to be a lowered metabolic rate in the nephrotic syndrome. This lowered rate, of

course, by no means indicates myxedema. The occasional and very unreliable effect of thyroid feeding in nephrosis is well recognized (10). In two of Davidson's cases there was no improvement on thyroid feeding, although one responded to parathyroid. Mention is made of a low serum protein in 3 of the 6 cases and in these 3 and in only these 3 was there ascites. In the case in hand dropsy on the basis of lowered osmotic pressure of the blood seems fairly well excluded by two normal values for the serum protein. There is no evidence that the fluid developed on the basis of an inflammatory type of nephritis. Tuberculosis, cirrhosis and carcinomatosis appear very unlikely in view of the favorable progress of the patient and the lack of any evidence that the fluid is returning. The remaining possibilities are that the fluid is the result of congestive cardiac failure, or that it is solely the result of thyroid deficiency. The former possibility is not easily excluded. A series of venous pressures* in which a constant level was maintained over a period of a month in spite of digitalis medication (which reached a full effect as evidenced by a prolongation of the P-R interval) is against the possibility of congestive failure. It is true that this level is in the range for doubtful or beginning congestive failure, but as a rule well marked congestion, in my experience, is not in evidence until the pressure is above 200 mm. of blood. Pressures in the upper limits of the normal range are seen in obese or edematous individuals in which the tension of the tissues about the vein is the contributing factor. The terminal fall in the curve seems attributable to the disappearance of subcutaneous myxedema fluid. Simple palpation revealed a striking change of this nature. Blumgart described normal venous pressures in 7 patients with myxedema in whom there were no signs of congestive failure.

Furthermore, it is very doubtful if congestive failure is part of the picture of a true myxedema heart. It does not appear in Zondek's original description (8), which includes only a slow pulse, enlargement (dilatation) of the heart and electrocardiographic changes. In none of his 7 cases is there definite evidence of congestive failure, and no mention is made of fluid in the abdominal or pleural cavities. The same applies to Assmann's case (13), the 3 described by Meissner (14), one by Means (15), 2 by Holzman (16) (although the second of these was said to have had a palpable liver and spleen, and the first a few rales at the right lung base). Pratt and Morton's one patient (17) was said to have died of heart failure. There is no mention of ascites being found at autopsy.

Willius and Haines in their study of 162 cases of myxedema denied the existence of a true myxedema heart and concluded that whatever cardiac difficulties were present were quite incidental. Of these 162 cases only one showed signs of definite congestive failure, and in that there was far advanced cardiovascular renal disease. In Christian's 32 cases (19), 12 showed heart lesions considered incidental to the myxedema present and

*Method described in Proc. Soc. Exper. Biol. & Med., **27**: 867. 1930.

not caused by it. None of these cases showed congestive failure or ascites. In 1928 (20) Christian stated that myocardial disturbance caused by thyroid deficiency and cured by thyroid feeding is relatively rare, while arteriosclerosis, coronary disease, etc., coincident with thyroid insufficiency, is much more common. Fahr (21, 22) was of the opinion that "myocardial weakness and heart failure are nearly always associated with hypothyroidism." His first subject with edema, enlarged liver, ascites, pulmonary rales and cardiac enlargement responding to thyroid but not to digitalis, he later admits was probably complicated by coronary sclerosis and hypertension. He reports 5 other cases all with the enlarged cardiac shadow, 3 of which have no signs of congestive failure. One of the others was considered probably complicated by nephrosis. Both of these 2 showed pulmonary rales, ascites and peripheral edema. From this survey we may conclude that the true thyroid heart is a rare phenomenon, and that when present it is rarely associated with congestive failure.

The high protein content of the ascitic fluid is not entirely unexpected. As far back as 1897 Magnus Levy (23) discovered that thyroid feeding caused a loss of water, a destruction of protein and to a lesser extent of fat. This occurred even with a high caloric diet disproving Richter's idea that the loss of protein was the result of insufficient nourishment. Magnus Levy believed there was a toxic destruction of body protein. Boothby, et al. (24), in studying the effect of thyroxin on 3 individuals, 2 of them myxedematous, concluded that there was a loss of myxedematous fluid and that this fluid was very rich in protein, containing about 2 per cent nitrogen. Deusch (25) has shown that the refraction, albumin content and viscosity of blood serum are increased in myxedema and decrease following treatment. In agreement with this, Kylin (26, 27) demonstrated high osmotic pressure values in two cases, one being 490 mm. of H_2O, the highest value he had seen in a large number of readings. However, this may not represent an actual protein storage, for Thompson (28) has shown that the plasma volume is decreased in myxedema and increases with treatment. Nevertheless Thompson (29, 30) himself has demonstrated that in most cases there is an elevation in the protein content of spinal fluid in myxedema (not, however, proportional to the severity of myxedema) with a fall under treatment. He attributes this to an increased storage of protein and nitrogen in myxedema. Falta (1) quotes Halliburton to the effect that protein bodies are in excess in the skin, parotid and blood. Etienne (31), et al., found an elevation of the blood urea nitrogen in 3 of 4 cases of congenital myxedema and in 3 of 6 cases of the acquired form with a return to normal following treatment.

The value of 5.1 gm./100 cc., found for the protein content of ascitic fluid in this case, compares with an average of 3.3 gm. which Epstein (32) found in 9 cardiac patients, the range being from 1.5-4.7. The protein content of cardiac ascitic fluid is higher than in any of the other forms of abdominal effusion. Salvesen and Linder (33) report the protein content

of ascitic fluid in two cardiac cases, one being 2.24 gm./100 for a case with nephrosclerosis and myocardial insufficiency and the other 2.6 in aortic insufficiency.

SUMMARY

A case is reported of well advanced myxedema presenting the unusual features of atony of the bladder, myxedema heart, and free fluid in the abdominal and pleural spaces. The fluid in the abdomen was found to have an unusually high protein content. It is believed that the atony of the bladder was a result of thyroid insufficiency and that the free fluid represented true myxedema fluid and not a manifestation of cardiac failure.

REFERENCES

1. Falta, W.: Handb. d. Inneren Medizin, Band IV, p. 442. 1912.
2. Barker, L. F.: Monographic Medicine, Vol. IV, p. 883. 1916.
3. Eppinger, H.: Handb. d. Neurol., Band IV, p. 100. 1913.
4. Scholz, W.: Spez. Pathol. und Therap. Kraus Brugsch, **I**: 533. 1919.
5. Souques, A. and C. Foix: Nouveau Traite de Medicine, Vol. VIII, p. 167. 1923.
6. Marine, D.: Practice of Medicine Tice, Vol. VIII, p. 231. 1921.
7. Janney, N. W.: Endocrinology and Metabolism, Vol. I, p. 379. 1922.
8. Zondek, H.: München med. Wchnschr. **65**: 1180. 1918. Ibid. **66**: 681. 1919.
9. Boothby, W. M.: Oxford Medicine, Vol. III, Part II, p. 942. 1930.
10. Fournier, M. J.: Bull. Acad. de méd., Paris, **93**: 691. 1925.
11. Marsh, H. E.: Am. J. M. Sc. **172**: 585. 1926.
12. Davidson, J. R.: Canad. M. A. J. **15**: 598. 1925. Ibid. **15**: 803. 1925. **16**: 1059. 1926. **17**: 161. 1928.
13. Assmann, H.: München. med. Wchnschr. **66**: 9. 1919.
14. Meissner, R.: München. med. Wchnschr. **67**: 1316. 1920.
15. Means, J. et al.: Bost. Med. & Surg. J. **195**: 455. 1926.
16. Holzmann, J. E.: Am. Heart J. **4**: 351. 1928.
17. Pratt, G. P. and H. B. Morton: Am. J. M. Sc. **173**: 274. 1927.
18. Willius, F. and S. Haines: Am. Heart J. **1**: 67. 1925.
19. Christian, H. A.: Rhode Island M. J. **8**: 109. 1925.
20. Christian, H. A.: Pennsylvania M. J. **32**: 70. 1928.
21. Fahr, G.: J. A. M. A. **84**: 345. 1925.
22. Fahr, G.: Am. Heart J. **3**: 14. 1927.
23. Magnus-Levy, A.: Ztschr. f. klin. Med. **33**: 269. 1897.
24. Boothby, W. M. et al.: Tr. A. Am. Physicians, **40**: 195. 1925.
25. Deusch, G.: Deutsches Arch. f. klin. Med. **134**: 342. 1920.
26. Kylin, E.: Ztschr. f. d. ges. exper. Med. **72**: 659. 1930.
27. Kylin, E.: Ztschr. f. klin. Med. **113**: 317. 1930.
28. Thompson, W. O. et al.: Arch. Int. Med. **44**: 368. 1929.
29. Thompson, W. O. et al.: J. Clin. Investigation, **6**: 257. 1928.
30. Etienne, et al.: Comp. rend. Soc. de biol. **92**: 1095. 1925.
31. Epstein, A. A.: J. Exper. Med. **20**: 334. 1914.
32. Salvesen, H. and G. Linder: J. Biol. Chem. **58**: 617. 1923.
33. Chaney, W. C.: J. A. M. A. **83**: 2013. 1924.

INSULIN ALLERGY

FRANK N. ALLAN, M.D.,
Division of Medicine, The Mayo Clinic,
and
L. RAYMOND SCHERER, M.D.
Fellow in Medicine, The Mayo Foundation,
ROCHESTER, MINNESOTA

The first preparations of insulin used in the treatment of diabetic patients frequently caused local irritation of the skin and subcutaneous tissues at the site of the injection. In a few cases there appeared general symptoms of an anaphylactic reaction. It was recognized that these conditions were due partly to chemical irritants contained in the extracts of pancreas, and partly to the presence of protein material. As methods of extraction and purification improved, such phenomena were observed less commonly. At present the ordinary commercial product possesses a purity approaching that of crystalline insulin. The development of the production of insulin by the manufacturers is a splendid record of achievement.

Because of the protein content of insulin, the possibility of trouble from anaphylactic shock was considered at the outset. Campbell wrote that when the first patient treated with insulin returned to the hospital with acidosis (the treatment having been interrupted because a supply of the extract was not available), precautions were taken to bring about desensitization. Campbell found, however, that in most cases sensitization phenomena were entirely absent. At the Toronto Clinic there was an occasional case in which urticaria was associated, but no serious case of protein sensitiveness was encountered. The initial reports of clinicians who participated in the early trial of insulin were similar. Wilder observed protein reactions in three cases in which the earlier preparations were used, but none with the later, more purified products. In his cases there was urticaria accompanied in two by circulatory changes. Joslin observed four cases in which urticaria developed. Williams recorded a case in which eruption of the skin accompanied by marked prostration developed suddenly and did not disappear completely for four days. In another case sensitivity was mildly manifested. Geyelin described symptoms resembling those of serum sickness in three cases.

Reports of cases of insulin hypersensitiveness have appeared sporadically. Cases in which cutaneous eruptions and other general symptoms of allergic reactions are associated have been described by Mauriac (1924); Lereboullet, LeLong, and Frossard (1924); Umber and Rosenberg (1924); Raynaud and LaCroix (1925); Achard and Bloch (1925); Walker (1926); Engelberg (1927); Tuft (1928); Jeanneret (1929); Bonem (1929); Hallermann (1930); Stroomann (1930); Kaufmann (1930), and Grishaw (1931). Von Noorden (1927) mentioned the occasional occurrence of such

cases, and Rackemann (1930) stated that he had seen two cases. The local irritation at the site of the injections which caused so much trouble when insulin was first introduced has apparently received little attention since then. In 1925, Lawrence stated that local insulin reactions of considerable severity occurred in 30 per cent of his cases; he considered the problem thoroughly. Joslin is quoted by Rackemann as observing local reactions in about 10 to 20 per cent of cases especially during the first few weeks of treatment, whereas systemic reactions which might be interpreted as "allergic" occurred about once among 1,000 diabetic patients. Recently Joslin stated that he saw allergic reactions less commonly. Other writers who have published reports concerning such reactions have described only one or two cases (5, 11, 16, 18, 30, 31). In most cases these reactions seem to have been relatively mild.

The incidence of hypersensitiveness to insulin in the cases of diabetes treated at The Mayo Clinic in the last four years is shown in table 1. In

TABLE 1
INCIDENCE OF INSULIN ALLERGY

	Patients Treated	Allergic Reaction	
		Cases	Per Cent
1927	428	14	3.2
1928	379	19	5.2
1929	360	29	8.0
1930	401	56	13.8
1931 January to June	206	29	14.1
1931 July to October	133	14	10.5

1927, it was recorded in 3.2 per cent of the cases; in 1928, in 5.2 per cent; in 1929, in 8.0 per cent, and in 1930, in 13.8 per cent. During the first six months of 1931 the high rate of 1930 was maintained. There were allergic reactions in 14.1 per cent of cases, but in the next four months the incidence fell to 10.5. It is probable that there were more cases in the earlier years, but even when allowance is made for many mild cases which might have been overlooked there is still a decided increase. We have been informed by other physicians that they have made a similar observation. If this situation is general the problem deserves widespread recognition and critical investigation. In our experience the occurrence of allergic reactions frequently constitutes an obstacle in treatment by insulin which cannot be ignored.

The reason for the increase in the number of cases in which allergic reactions occur is not known. Since more of the patients who come for treatment now have been treated with insulin previously, it is possible that sensitization may have occurred on this account. Yet, even in cases in which insulin has never been administered, hypersensitiveness is more

common. A change in the quality of insulin may be suspected. The manufacturers state that there has been no significant change in the method of preparation. Yet there appears to be variability in the behavior with different lots of insulin. The incidence of allergic reactions varies greatly from month to month. There are also differences in the experience of different physicians. Some seem to have little trouble with allergic reactions; others encounter them frequently. Most of our experience has been with the products of one company. However, we have used insulin made by the four firms manufacturing it in this country, and have found allergic reactions with all. It would be desirable to have exact figures on the relative incidence with different preparations.

An analysis of the nature of the allergic reaction in the last 100 cases is shown in table 2. In eighty-four cases there was a mild local reaction

TABLE 2
RESULTS IN CASES OF INSULIN ALLERGY

	Group 1	Group 2	Group 3	Total
Desensitization	7	1		8
Relief with change of insulin	59	5		64
Persistence of symptoms; insulin treatment continued	5	1		6
Persistence of symptoms; insulin treatment stopped	13	5	4	22
Total	84	12	4	100

Group 1—Mild local reaction.
Group 2—Severe local reaction.
Group 3—General symptoms in addition to local reaction.

at the site of the injection; in twelve cases there was a severe local reaction, and in four cases there were general manifestations of an allergic reaction, as well as local signs. In addition two patients reported that after they had left our observation the local reaction, which was present persistently, was temporarily complicated by a generalized eruption of the skin.

The mild local reactions are usually characterized by stinging, smarting, or burning pain at the time of the injection, followed in an hour or two by the appearance of swelling of the tissues and redness of the skin. The redness may cover an area of 1 to 4 cm. in diameter. There may be a slight wheal or extensive induration of the skin and subcutaneous tissues forming a nodule 1 to 3 cm. in diameter. The lesion is usually accompanied by burning and itching. Sometimes there is intense burning and itching when neither redness nor swelling can be seen. The pain and irritation may be very annoying and distressing. The reaction reaches its maximum in twelve to twenty-four hours and gradually disappears in from one to three days.

The severe local reactions present the same manifestations in an exaggerated degree. There is intense inflammatory change at the site of the injection, with the formation of a hard, tender swelling which may be 5

to 8 cm. in diameter. The skin feels hot, and may be red over an area of 15 cm. in diameter. The burning pain may be almost unbearable. In a few cases there have been fever and malaise. In certain exceptional cases the formation of a sterile abscess has been reported. The lesion usually begins to appear within an hour after the injection, but may be delayed until the following day. It usually subsides within a week, but may not completely disappear for several weeks.

The local reaction usually becomes manifest between the third and fourteenth days after beginning of treatment. It is uncommon for a patient to have an allergic reaction with the first injections. If, however, a hypersensitive patient has had previous treatment which has been interrupted, there may be a reaction immediately on resuming the injections. If insulin has been used continuously for two weeks without trouble, it is rare for any allergic manifestation to appear.

The general allergic reaction to insulin is manifested by cutaneous, circulatory, and sometimes gastro-intestinal symptoms. Urticarial eruptions and edema are the common cutaneous changes. In one case we have observed generalized dermatitis. Before the eruption appears there may be numbness, tingling, and itching of the parts affected. Pruritus becomes intense. There may be swelling of the mucous membranes of the mouth and also of the larynx, causing respiratory embarrassment. Pallor, flushing, and palpitation appear at the beginning, and may be quickly followed by circulatory collapse with subnormal blood pressure, weak pulse, and general prostration. Nausea, vomiting, and abdominal cramps may occur but are not common. The severe symptoms usually subside within an hour or two, but there may be prostration of some degree for several days. There has so far been no report of fatality directly due to insulin allergy. The general reaction described may occur if patients have been receiving insulin for at least a few days, or who have recommenced treatment after a period of cessation. It does not occur with the initial treatment. There is almost always local reaction before the appearance of general symptoms.

Local reaction at the site of injection may depend on chemical irritation as well as on allergy. Irritation of the former type was frequent with the early crude preparations of insulin which contained a high concentration of salts, or excessive amounts of tricresol used as a preservative. In addition, acidity of these preparations undoubtedly caused much of the stinging which was felt so commonly. Insulin must be kept in slightly acid solution since it is unstable in neutral or alkaline solution, but some of the early preparations were excessively acid. There are perhaps some patients who are hypersensitive to the degree of acidity which is tolerated by the average patient. Such patients may be relieved of irritation if the insulin is neutralized before injection. We have tried this procedure in many cases. It was found satisfactory in two cases in 1926, but has not prevented irritation in cases treated since then. Neutralization of insulin was also tried by Stilwell in 1924. Another condition which must be dis-

tinguished from insulin allergy is irritation from denatured alcohol used for sterilization of the skin. In one of our cases it was found that irritation was due to hypersensitiveness toward the formalin contained in the alcohol.

That the hypersensitiveness to insulin under consideration may be a true allergic phenomenon has been demonstrated by several investigators. In 1925, Raynaud and LaCroix demonstrated the transfer of insulin hypersensitiveness to a guinea pig by injecting it intradermally with serum of a patient. Insulin injected in the area of skin affected by the serum caused local reaction, while injections elsewhere were innocuous. They also demonstrated the presence of precipitins for insulin in the patient's serum. These observations were confirmed in 1928 by Tuft, who carried out further immunologic studies. He brought about local passive transfer of hypersensitiveness to the skin of other persons, and showed that the reactions to insulin protein demonstrated by this procedure disappeared in four months after the occurrence of the reaction. He found that with the exception of precipitins, which were present only for a short time after the reaction, other types of antibodies were not demonstrable. Campbell, Gardiner and Scott also reported local passive transfer of hypersensitiveness. Barral, and Rous, in 1931, gave further demonstration that insulin is in itself a specific antigen through experiments on guinea pigs. They produced specific sensitization for serum, pancreas emulsion, and insulin. The sensitization to insulin was distinct, although much less than that produced toward the other agents.

The purest preparations of commercial insulin contain a small amount of protein. Even crystalline insulin is not free from protein; it is a polypeptid at least. It is probable that insulin contains two kinds of protein; one part which is characteristic of the hormone, and the other part another pancreatic protein which varies with the species. The basis for this opinion is the fact that certain patients are sensitive to all types of insulin including crystalline insulin. In these cases there is probably sensitiveness toward the hormone protein. Other patients are sensitive only to insulin derived from one kind of animal. In such cases there is probably sensitiveness toward the pancreatic protein of the species. The sensitiveness toward the pancreatic protein is not associated with sensitiveness to other proteins from the same animal. A patient who manifests an allergic reaction to beef insulin, for example, does not manifest sensitiveness to beef muscle protein. It is assumed that crystalline insulin represents the pure hormone. The fact that a patient may become hypersensitive toward it, must indicate, however, that it contains something different from his own insulin. It would presumably be impossible for him to become hypersensitive to a material which is produced in his own body. The occurrence of the allergic reactions toward crystalline insulin then shows either that it is not the pure hormone, but the hormone plus a protein, or that the hormone itself is a protein which is different in different species.

Skin tests may be employed in the investigation of insulin allergy, and are of value under two circumstances. If a patient who has been previously treated by insulin gives a history of allergic manifestations, an intracutaneous test may be made to determine if he is still hypersensitive before again resuming treatment. The test might be used, too, to determine the existence of insulin allergy when it is suspected in a case in which irritation of the skin from the usual injections has not been noticed.

In all of our cases of insulin allergy in which intracutaneous tests were made, the result was strongly positive. However, in certain cases, in which there was no evidence of hypersensitiveness to the therapeutic injections of insulin, the skin tests were distinctly positive, although less marked. The significance of such skin reactions is under investigation. The chief value of intracutaneous tests is not for the recognition of insulin allergy, but to guide attempts at treatment. Skin tests made with various preparations of insulin may show variable degrees of hypersensitiveness, or absence of hypersensitiveness to some preparation. A preparation which does not cause reaction or a minimal reaction can then be chosen for use in treatment.

The results obtained in dealing with our 100 cases of insulin allergy are summarized in table 2. The cases are classified in three groups. As noted, in eighty-four cases there was mild local reaction, in twelve cases there was severe local reaction, and in four cases there were general symptoms in addition to local reaction.

In eight cases desensitization was spontaneous. The usual injections of insulin were continued and the local reaction gradually diminished and disappeared. The duration varied from a few days to a number of weeks. In only one of these cases was the local reaction severe at the beginning; in the remainder the irritation was mild. An interesting point in regard to desensitization toward insulin is that the change may be localized to the area where the injections are customarily made. A patient who had become free from local reactions complained that the trouble had recurred when he entered hospital at a second visit. It was found that the reaction occurred on the arms where the injections were given by the nurses, but not on the thighs where he had been accustomed to give the injections himself. A similar observation was made by the patient whose experience was reported by Campbell, Gardiner and Scott. Our efforts to bring about desensitization deliberately have not been very effective, although in certain cases there may be some benefit. In one case, which will be described later, partial desensitization was of great value in carrying a patient with a serious allergic reaction through a dangerous emergency.

In sixty-four cases there was relief with change of the type of insulin; in five of these the reaction had been severe, and in fifty-nine mild. At the beginning various preparations of insulin were tried until a non-irritating product was found. Recently intracutaneous tests with the various preparations have made it possible to select quickly the type of insulin best to

employ. In some cases change of the insulin gave immediate and complete relief; in a few cases the reaction was lessened but not completely relieved at the beginning. It is probable that the majority of the patients in this group would have become desensitized spontaneously if the treatment had been continued. Yet the early relief secured by change of insulin saved them distress and discomfort.

In six cases in which the treatment by insulin must be continued there is still trouble with irritation from the injections, and, as yet, no means of treatment has given satisfactory relief. In one case the local reaction is severe and distressing, and there appeared a transitory urticarial skin eruption after the patient had gone from observation. In the other cases the irritation, although annoying, does not cause any appreciable hardship.

In twenty-two cases there was persistent trouble from injections of insulin, until the treatment could be stopped. In five of these cases reactions were severe and in four, symptoms were general. The patients in this group were fortunate in having mild diabetes so that treatment by insulin was needed only, temporarily at the beginning of treatment, or at the time of some complication or operation. In most cases the patient endured the trouble from the injections until the need for insulin had passed.

As may be seen from this review, our efforts to deal with local reactions from insulin are not very satisfactory except in the cases in which a change in the type of insulin gives relief. In the remaining cases the patient must usually bear the discomfort until he becomes desensitized spontaneously, or until insulin can be stopped. Soothing lotions may be used to make the condition tolerable; 1 per cent solution of menthol in alcohol has proved helpful. In cases of severe inflammatory reaction, hot compresses must be applied continuously. Calcium has been tried; in our experience it does not seem to be effective. Mixture of insulin with a local anesthetic such as novocain, is of practically no value. It may check the immediate pain following the injection, but does not prevent the inflammatory reaction and the pain which comes later. It is fortunate that in so many cases continuous treatment with insulin is unnecessary. Certain cases of severe allergic reaction merit more detailed report:

Case 1. Severe general allergic reaction, partial desensitization to permit control of diabetes when aggravated by an operation. This case which presented the greatest difficulty in treatment was that of a woman, aged forty-eight years, who was found to have diabetes in October, 1923. She was a woman of nervous temperament, and had suffered from urticaria and hay fever at times since childhood. Her father had asthma.

Diabetes was mild and was readily controlled by dietary restriction under ordinary circumstances. In 1924, she had had a pelvic operation, and at this time insulin was given for a short time to control the aggravation of diabetes which followed. The injections caused a mild local reaction. In August, 1927, during treatment of varicose veins, insulin was given again. The first injections caused a severe local reaction which increased in intensity. On the fourth day a severe general reaction occurred. There was diffuse urticaria with marked edema affecting the face particularly; the eyes could hardly be opened. There was swelling of the mucous membranes of the mouth and throat, so that breathing

became difficult. These changes were accompanied by marked prostration. Insulin was stopped. Temporary relief was given by injections of epinephrine, but for three days the patient was in great distress.

In December, 1930, the patient was admitted to hospital with empyema of the gallbladder. Diabetes was aggravated at the time so that on admission the urine contained sugar and the concentration of sugar in the blood was 200 mgm. in each cubic centimeter. Because of the former experience intracutaneous tests were made before giving insulin, using preparations from four different sources and three different species, cattle, pigs and sheep. A marked reaction occurred at the site of each injection; there was a large wheal surrounded by a flare about 6 to 7 cm. in diameter. General symptoms, palpitation, weakness, and paresthesia affecting chiefly the lips, were also present.

Operation was considered imperative, and the gallbladder was removed December 19, even though glycosuria was not controlled. After the operation the condition became more serious. Acidosis developed. The carbon dioxide combining power of the blood plasma fell to 21.1 volumes per cent two days later; the value for sugar in the blood was 295 mgm. in each cubic centimeter. A supply of solution of crystalline insulin, obtained from the University of Toronto through the courtesy of Dr. D. A. Scott, arrived at this time. A skin test showed that marked hypersensitiveness to this insulin existed also, but it was much less than that observed with the ordinary commercial preparations. In spite of the fear of the collapse from allergic shock, administration of the crystalline insulin was begun, since the danger of coma was threatening. The first dose given at 1:00 P.M. was 1 minim of a 1 in 10 dilution of the insulin, which contained 40 units in each cubic centimeter. The dosage was repeated at intervals of half an hour, being increased 50 per cent each time unless the irritation from the previous injection was too great. At 7:00 P.M. the dosage reached 25 minims of the 1 in 10 dilution (approximately 3 units). This dosage was repeated hourly during the night. At 5:00 P.M., four hours after beginning treatment the carbon dioxide combining power was 24.9 volumes per cent, at 9:00 P.M. 39, and the next morning it was 64.5. The clinical condition was correspondingly improved. The patient had been critically ill, but now looked and felt well.

December 22, the dilution of insulin was changed to 1 to 2. This was tolerated with little reaction, and December 29, undiluted crystalline insulin was used with practically no irritation. Diabetes was controlled in a satisfactory way, and from this time on the patient made good progress. The daily requirement of insulin was from 40 to 50 units. Since the supply of crystalline insulin was limited, efforts were made to desensitize the skin toward one of the commercial preparations. To begin with, 1 minim of a 1 in 10 dilution was used, the dosage being gradually increased. It was finally tolerated with only a little irritation. Improvement continued so that January 10 insulin treatment was discontinued. Eleven days later, skin tests were again made. There was immediate, severe, local reaction. Generalized itching of the skin followed; the lips felt stiff and the heart rate increased. These symptoms disappeared in an hour, but pruritus persisted for four days. There was thus return of extreme hypersensitiveness. Fortunately insulin was no longer needed to control diabetes.

Case 2. Severe generalized allergic reaction to insulin, resulting in complete intolerance to treatment. A man, aged forty-six years, came to the clinic in January, 1931. Diabetes had been discovered in 1927. At the beginning he received a series of six injections of insulin. They were given at intervals of several days, the last three being given in the same week. Following the final injection, a skin eruption appeared. The skin became red over the entire body, and there was intense burning. The patient said that he felt as if he were on fire. The eruption subsided in a few days and no further attempt was made to continue treatment with insulin.

Because of this history, investigation of sensitiveness toward insulin was made when the patient came for consultation to the clinic. Intradermal skin tests were made with various types of insulin, using insulin made by five manufacturers from pig, beef and sheep parcreas and also a solution of crystalline insulin. Very strongly positive reactions resulted from all tests. There was immediate formation of a wheal at the site of the injection, with a large flare about it. There was also generalized itching of the skin which did not disappear entirely for a week.

Fortunately for the patient, the diabetes was of such a mild nature that it could be controlled by diet. However, if the condition should become severely aggravated by sickness or operation, the same serious situation as occurred in case 1 might be encountered.

Case 3. Urticaria following treatment with insulin. A woman, aged forty years, came to the clinic in June, 1930, because of loss of weight for three weeks. Diabetes was discovered and treatment with insulin was commenced. Ten days after beginning treatment she complained of painful swelling at the site of injection. At the same time she noticed an itching sensation over her entire body. The following day urticarial wheals appeared on her forehead and then spread over the entire body sparing the palms. Itching was intense. It was relieved temporarily by epinephrin administered subcutaneously. Fortunately it was possible to discontinue the insulin without return of glycosuria. The skin eruption disappeared in a few days. Intradermal skin tests revealed a strongly positive reaction to the pork insulin used. There was a slightly positive reaction to beef insulin.

This patient gave a history of allergic manifestations. She was sensitive to strawberries and once severe urticaria had developed following the use of quinine.

Case 4. Local irritation and generalized urticarial eruption following treatment with insulin. A woman, aged fifty years, had diabetes which was discovered in 1924, although symptoms had been present for several years previously. The disease was usually mild, but it had been necessary to use insulin in November, 1926, following amputation of the breast for carcinoma. The insulin was tolerated for almost two months, and then local and general reaction developed. There was itching, pain and swelling at the site of injection. This continued for three weeks, and then insulin was discontinued. Three days after the treatment was stopped the reaction had entirely disappeared.

The patient returned in March, 1931, because of a diseased gallbladder. She had not received insulin for five years, although glycosuria was never under control. Since the urine contained a large amount of sugar, insulin was given. It was tolerated well for five days; then a large itching swelling appeared at the site of injection. Intradermal skin tests revealed that there was sensitiveness of varying degree to all types of insulin but only a slight reaction to beef insulin. This was administered and the irritation from the injections was negligible at first. Six days later urticarial wheals appeared on the knees, hands and back of the neck. They disappeared in a few days, but local irritation at the site of injection continued to give trouble. It still occurred when a third type of insulin was used. Application of menthol and alcohol helped to make it tolerable. The treatment could not be stopped as, following operation for removal of the gallbladder, the diabetes was aggravated, necessitating even larger doses of insulin. Two weeks later improvement took place so that treatment could be stopped, but the irritation remained until the injections were discontinued.

The patient did not give a history of allergic manifestation. However, her mother had had severe asthma.

Case 5. Generalized dermatitis with intolerance toward all types of insulin. A woman, aged fifty-seven years, had had diabetes for about six years. It was partially controlled by diet, but the urine usually contained sugar. Treatment with insulin was commenced in July, 1927. In October, 1927, after receiving a new supply of insulin, she noticed that an erythematous wheal developed in the right thigh at the site of the injection. The skin was painful and itching. Later, injection in the left thigh had the same effect, but the reaction gradually disappeared.

In December, 1927, dermatitis appeared on the arms and thorax and spread over the entire body, except for the head and neck. There was erythma with slight desquamation, and the patient suffered intensely from itching and burning. Treatment with insulin was given intermittently. The dermatitis and pruritus subsided when the treatment was stopped, but returned when insulin was given again. Different types of insulin were employed, and it seemed at first that insulin made from beef pancreas had caused less reaction, but later there was no difference.

The relationship of insulin treatment to the condition of the skin was not absolutely certain at first. Intracutaneous tests were not made in this case. Yet the invariable return of dermatitis when insulin was given and subsidence with withdrawal were convincing. The patient had moderately severe diabetes, which could not be controlled completely by diet. Because of her inability to tolerate insulin she was in poor health constantly. Death occurred from cerebral hemorrhage in August, 1930.

Case 6. Severe local allergic reaction to insulin, failure of attempts to obtain relief by desensitization or by change of the type of insulin. A woman, aged

forty-two years, was found to have diabetes in August, 1930, when she came to the clinic for treatment of carcinoma of the cervix. Glycosuria was easily controlled by diet, at first. Following roentgen-ray treatment for carcinoma, the diabetes became aggravated and treatment with insulin was commenced. On the fifth day of treatment a severe local irritation appeared at the site of injection. The type of insulin was changed and partial relief resulted. Insulin was soon discontinued and diet alone sufficed.

The patient returned in February, 1931, for hysterectomy, and following the operation insulin was again needed. Intradermal skin tests were made to determine which type of insulin would be best tolerated. There was irritation of varying degree from all types, yet, for three days the injections were well tolerated. Then a severe local reaction recurred. Painful, red swellings, 3 or 4 cm. in diameter, appeared at the site of each injection. The treatment was interrupted for four days, but when insulin was given again, using a third type, the same reaction returned, and the pain was intolerable. An addition of 2 per cent solution of novocain to the insulin was made; this gave temporary relief, but in a few hours after the injection the pain was as severe as before. It was necessary to cease the insulin treatment, but fortunately diabetes could be controlled with more drastic restriction of the diet.

This patient gave a history of allergy; she had the type of hay fever that occurs in autumn, and her father had both asthma and hay fever.

A case described by Campbell, Gardiner and Scott came under our observation. They wrote concerning the case: "One patient shows marked sensitivity to beef, hog, sheep, fish and human insulin obtained from different sources. He is also sensitive to crystalline insulin, though the reaction is less intense. The sensitivity can be locally communicated to other individuals by passive transfer. He has now developed local desensitization on a part of one thigh for crystalline insulin only." Later there was complete desensitization. The difficulty in dealing with this case, and the successful outcome which followed the investigation of Campbell, Gardiner and Scott, make it noteworthy. The information concerning the case was supplemented by a report received from Munro:

The patient was a young man, aged twenty-two years. A diagnosis of diabetes was made following an examination for insurance in 1923. The condition was mild at first, but December 26, 1929, it became necessary to begin treatment with insulin. After ten days' treatment, there was a severe inflammatory reaction at the site of injection in the leg. There was redness of the skin, involving an area 12 cm. in diameter; it was extremely painful and itching. Each injection was followed by a similar reaction. January 7, pork insulin was used in place of beef insulin, but the reactions were unchanged. January 8, a solution of crystalline insulin was used. There was a local reaction 4 to 6 cm. in diameter, but there was much less swelling and absence of pain. Crystalline insulin was then used regularly, since attempts to use ordinary insulin were followed by much more severe local reaction. An injection of 5 units of beef insulin given January 19 caused diffuse swelling of the thigh with swelling and tenderness of the inguinal lymph nodes. January 22, cutaneous tests were made with several varieties of insulin including beef, pork, sheep, human and fish. There was severe reaction with every type. Meanwhile the reaction to solution of crystalline insulin became less and disappeared.

October 1, an attempt was made to bring about desensitization toward ordinary beef insulin. One minim was mixed with the usual dose of 15 units of crystalline insulin; there was slight reaction. The amount of beef insulin mixed with the crystalline insulin was increased 1 minim each day for ten days. There was practically no reaction, and at the end of this time it was possible to use ordinary beef insulin alone in the desired dosage. Treatment with this insulin was continued, the injections being given only in the thighs. In November an injection given in the arm caused severe local reaction. There had evidently been desensitization of the skin of the thigh only. In the course of three months, however, it became possible to administer insulin in the arm without reaction. Since that time insulin has been used regularly without difficulty.

In none of our cases was there any interference with the effect of insulin on diabetes. The condition responded to treatment in the usual way. Cases of diabetes which are relatively refractory to insulin are occasionally encountered. Glassberg and his co-workers reported a striking example in 1927, and mentioned the possibility that an allergic phenom-

enon might account for it, since the patient earlier had had skin irritation from the injections. However, the relationship was not considered probable. Although we have seen a number of these patients, requiring several hundred units daily, the abnormal behavior can be attributed to allergy in none (2).

There are four cases on record in which allergy is credited with interference with the action of insulin. In a case reported by Williams, a boy with severe diabetes had acidosis. He was given insulin, but for eight days remained in acidosis, suffering from marked prostration, abdominal cramps and vomiting. The kind of insulin used was changed, extract from beef pancreas being used in place of extract from pig pancreas. Recovery occurred in forty-eight hours. Williams concluded: "Since no treatment was instituted to bring about this remarkable result other than changing from insulin of pig origin to that of beef, it is a fair inference that the patient was suffering from an allergic attack involving the pyloric end of the stomach and due to pig protein." Yet this clinical picture and similar delay in recovery from acidosis may be seen without allergic disturbance. It was observed, for example, in a case seen in consultation by one of us in which there was no question of allergy. The patient was treated in hospital for ten days, but remained in a semistuporous condition with abdominal pain and vomiting. Insulin was given, but seemed to be ineffective. The administration of insulin was then changed to give a comparatively small dose at regular intervals (15 units every six hours) and glucose was given intravenously; with better spacing of the injections, effective control of diabetes resulted and the patient recovered from the acidosis in twenty-four hours. In a case such as that of Williams a skin test might be used to support the inference that the difficulty in treatment was due to allergy.

Karr, Kreidler, Scull and Petty observed a case of unusual interest. A patient who had marked sensitivity to insulin persisting throughout twenty months of treatment by insulin, began to require more and more insulin so that in fourteen months 600 to 700 units were given daily. Intradermal tests with insulin from pig pancreas, beef pancreas and also solution of crystalline insulin caused a typical wheal to form, and a precipitin test with the patient's serum and insulin was positive. Using the patient's serum as the activating antigen, rabbits were sensitized and the patient was then treated with rabbit serum. A week later the dosage of insulin was reduced from 650 units to 150 units; in a month it was possible to discontinue insulin, and diabetes became latent. The local reaction to insulin was unchanged.

Rudy described a case in which urticaria was followed by acidosis with resistance to insulin in a case of mild diabetes, in which 5 units of insulin were given daily. A total of 515 units of insulin was given on the first day after admission to hospital, and on successive days, 270, 170, 140, 80, 40 and 10. Insulin was stopped on the eleventh day, and subsequently diabetes was mild enough to permit control with dietary treatment. The

origin of the urticaria was unknown. Insulin was mentioned as a possibility, but evidently was not given serious consideration. The resistance to insulin was attributed by Rudy to the interference with the function of the skin with respect to carbohydrate metabolism. In this case, as in that of Williams, an intracutaneous test might have helped to determine the existence of insulin allergy.

A puzzling case was reported by Foerster: A man, aged sixty-seven years, had had diabetes for twenty-five years. It was treated by restriction of the diet, yet the urine usually contained acetone and 2 per cent sugar. An attack of erysipelas occurred. Insulin was given to control diabetes and injections of milk were given for treatment of erysipelas. Several days later transitory urticaria appeared. Insulin was given for five weeks and the treatment was then abandoned. After several months, treatment of diabetes was again begun, and insulin was used, the dosage being 60 units daily. At the beginning of the second week there was a sudden change. Glycosuria increased remarkably and acidosis developed. Later urticarial eruption appeared. Huge doses of insulin were given, but without apparent effect on acidosis. It was decided that the insulin was doing no good and treatment was stopped. A vegetable diet was given, and then on the third day an oatmeal diet. The condition of the patient improved and acetonuria ceased. After a week the patient was taking food containing 70 gm. of carbohydrate, 60 gm. of protein and 100 gm. of fat, with 30 gm. of sugar appearing in the urine each day. Further trial was given to insulin, but 30 units did not cause any reduction of the glycosuria. A different kind of insulin was employed and 40 units were given. There was again no change in the excretion of sugar.

Foerster concluded that because of anaphylaxis the injection of insulin resulted in interference with the action of the endogenous insulin as well as of that administered. He thought that the interruption of the administration of insulin permitted return of activity of the endogenous insulin, although there was still no response to injected insulin.

SUMMARY AND CONCLUSIONS

Our experience shows that hypersensitiveness to insulin is not uncommon, occurring in approximately one of eight to ten of our cases. In four of 100 consecutive cases hypersensitiveness was manifested by generalized symptoms of anaphylaxis. In eighty-four cases there was only a mild reaction at the site of injection, which was usually relieved by a change of the type of insulin or by spontaneous desensitization. In twelve cases there was a severe local reaction with less relief by change of insulin. These cases and the 4 per cent of cases in which symptoms were general presented difficult problems in treatment. Fortunately no case was encountered in which diabetes became refractory to insulin because of allergy.

The cases reported in which failure of insulin to exert its usual effect was attributed to allergy indicate the danger which may result from this phenomenon. How should such cases be treated? Failure to give insulin

may lead to death from acidosis if diabetes is severe. Use of insulin may cause danger from anaphylactic shock. The following policy seems wise. Attempts should be made to control diabetes by diet if possible. If this cannot be done, insulin must be employed. The danger from failure to receive it exceeds the danger which may result from anaphylaxis, or from possible development of antibodies toward it. This opinion may require modification, but is justified by our present knowledge and experience. If there is no type of insulin free from allergic effect, attempts should be made to bring about desensitization by beginning treatment with minimal dosage and increasing the amount gradually. If acidosis develops, and if diabetes becomes refractory, the dosage of insulin should be increased. Any other policy is dangerous. So long as the urine contains sugar and acetone bodies, more insulin should be employed. Whenever resistance to insulin is encountered from any cause, attention to this rule may save life.

The occurrence of allergic manifestations after treatment with insulin throws some light on the nature of the hormone. It indicates that the protein of animal insulin is different from the protein of human insulin. Furthermore, the hypersensitiveness, sometimes shown toward insulin from one species with tolerance toward insulin from another, suggests that the pancreatic extracts contain another pancreatic protein besides insulin.

REFERENCES

1. Achard, C. and Sigismond Bloch: Diabéte avec coma guéré par l'insuline. Accidents d'anaphylaxie et pychémie consécutive. Bull. et mém. Soc. méd. d. hôp. de Paris, **2**: 1210. 1925.
2. Allan, F. N. and G. R. Constam: Insulin resistance in a case of bronze diabetes. Med. Clin. North America, **12**: 1677. 1929.
3. Barral, P. and J. Rous: L'insuline constitue-t-elle en elle-même un antigène spécifique? Compt. rend. Soc. de biol. **106**: 292. 1931.
4. Bonem, P.: Nebenwirkungen von Insulin. München. med. Wchnschr. **76**: 1585. 1929.
5. Campbell, W. R., W. J. Gardiner and D. A. Scott: Reactions after administration of crystalline insulin. J. Clin. Investigation, **9**: 28. 1930.
6. Engelberg, J.: Ein Fall von Insulinanaphylaxie. Med. Klin. **1**: 212. 1927.
7. Foerster, E.: Ein Fall von paradoxer Insulinwirkung. Med. Klin. **1**: 846. 1926.
8. Geyelin, H. R., G. Harrop, M. F. Murray and Eugenia Corwin: The use of insulin in juvenile diabetes. J. Metab. Research, **2**: 767. 1922.
9. Glassberg, B. Y., M. Somogyi and A. E. Taussig: Diabetes mellitus. Report of a case refractory to insulin. Arch. Int. Med. **40**: 676. 1927.
10. Grishaw, W. H.: Allergic manifestation to insulin. J. A. M. A. **97**: 1885. 1931.
11. Hajek, J.: Local insulin reaction. J. A. M. A. **96**: 193. 1931.
12. Hallermann, A.: Nebenerscheinungen bei der Insulinanwendung. Deutsche. med. Wchnschr. **56**: 1611. 1930.
13. Jeanneret, René: Une application pratique de la méthode de désensibilisation par les cuti-réactions répétées. Urticaire a l'insuline. Rev. méd. de la Suisse Rom. **49**: 99. 1929.
14. Joslin, E. P., H. Gray and H. F. Root: Insulin in hospital and home. J. Metab. Research, **2**: 651. 1922.
15. Joslin, E. P.: Personal communication to the authors.
16. Karr, W. G., W. A. Kreidler, C. W. Scull and O. H. Petty: Certain immunologic studies in insulin sensitivity. Am. J. M. Sc. **171**: 293. 1931.
17. Kaufmann, E.: Nebenerscheinungen bei der Insulinanwendung. Deutsche. med. Wchnschr. **56**: 1955. 1930.
18. Lasersohn, M.: Local insulin reactions. J. A. M. A. **95**: 199. 1930.
19. Lawrence, R. D.: Local insulin reactions. Lancet, **1**: 1125. 1925.
20. Lereboullet, P., M. Lelong and R. Frossard: Un cas de diabéte infantile traité par l'insuline avec accidents cutanés graves: l'érythrodermic oedémateuse insulinienne. Bull. et mém. Soc. med. d. hôp. de Paris, **2**: 1184. 1924.
21. Macleod, J. J. R. and W. R. Campbell: Insulin. P. 77. Williams and Wilkins Co., Baltimore. 1925.
22. Mauriac, M.: Quoted by Blamoutier, P.: Un cas de sensiblization à l'insuline chez une petite fille. Paris méd. **53**: 372. 1925.

23. Munro, J. A.: Personal communication to the authors.
24. von Noorden, K. H. and S. Isaac: Die Zuckerkrankheit und ihre Behandlung. Pp. 494-495. Julius Springer, Berlin, 1927.
25. Rackemann, F. M.: Clinical allergy, particularly asthma and hay fever. P. 192. MacMillan Co., New York, 1931.
26. Raynaud, M. and Adrien LaCroix: Un cas d'anaphylaxie à l'insuline. Essai de pathogénis des oedémes insuliniens. Bull. et mém. Soc. med. d. hôp. de Paris, **1**: 831. 1925.
27. Rudy, A.: Urticaria and insulin resistance with reference to the relation of the skin to the carbohydrate metabolism. New England J. Med. **204**: 791. 1931.
28. Stilwell, G. R.: Neutralization of insulin before injection. Brit. M. J. **2**: 465. 1924.
29. Stroomann, G.: Anaphylaktische Erscheinungen nach injektion. von Insulin (A. B. Brand). Med. Klin. **2**: 1523. 1930.
30. Sturtevant, M.: Local anaphylaxis following injection of insulin. J. A. M. A. **82**: 964. 1924.
31. Tuft, L.: Insulin hypersensitiveness; immunologic considerations and case reports. Am. J. M. Sc. **176**: 707. 1928.
32. Umber, F. and M. Rosenberg: Weitere Erfahrungen mit Insulin an 100 klinisch behandelten Diabetikern. Deutsche. med. Wchnschr. **50**: 359. 1924.
33. Walker, S. E.: Report of a case of diabetes mellitus with anaphylaxis following the hypodermic injection of insulin. U. S. Vet. Bur. M. Bull. **2**: 700. 1926.
34. Wilder, R. M., W. M. Boothby, C. J. Barborka, H. D. Kitchen and S. F. Adams: Clinical observations on insulin. J. Metab. Research, **2**: 701. 1922.
35. Williams, J. R.: Allergic insulin reactions. Report of a case exhibiting severe gastro-intestinal allergic reactions following injections of insulin. J. A. M. A. **94**: 1112. 1930.

A NOTE ON THE RELATIONSHIP BETWEEN NYSTAGMUS DURATION AND THYROID CONDITION

O. H. MOWRER AND W. R. CASEY
From the Psychology Laboratory of the Johns Hopkins University
BALTIMORE

For many years the duration of post-rotation nystagmus was regarded by clinical otologists as a highly reliable index of the functional integrity and general sensitivity of the so-called vestibular apparatus of the inner ear. However, it has been found that nystagmus time varies so greatly from individual to individual and in a given individual from time to time that such measurements are likely to be very deceptive (8).

As early as 1914 Güttich (7) called attention to the fluctuation in the nystagmus time of the same individual on different occasions, and ascribed a prominent share in the causation of this fluctuation to changes in the emotional state of the subject. More recently Detlefsen (4), Boenninghaus (2), Fenton (6), and others have discussed the variability of nystagmus duration and have likewise emphasized the apparent influence of emotion and excitement. Other writers (3) have noted a correlation between nystagmus duration and certain abnormal mental conditions; but nowhere, apparently, has there been proposed a definite and specific physiological explanation of how and why the observed nystagmus-time variations occur.

Since the secretion of the thyroid gland is usually regarded as having a positive influence on general nervous irritability (9) and since nystagmus duration is commonly supposed to depend specifically on vestibular irritability (10), it would seem reasonable to assume that the fluctuations in the nystagmus time of a given individual on different occasions might possibly be due to concomitant changes in thyroid condition. If such an hypothesis could indeed be established, nystagmus time would afford a very convenient means of ascertaining, not only the temporarily prevailing thyroid condition of the organism, but also chronic conditions of thyroid malfunctioning (1).

In order to test this hypothesis, the writers devised the following simple experiment. Fourteen healthy adult homer pigeons were carefully tested on three successive days for nystagmus time, weight, and pulse rate. These birds were then equally divided into two groups in such a way that the average value for each of the three items just mentioned was closely comparable for both groups. Beginning on the evening of the third day, one group was force-fed 1/20 gr. of desiccated thyroid every morning and evening for two weeks. The remaining control group was given no thyroid, but otherwise subjected to exactly the same treatment. The birds lived together in a large cage with ample space for exercise and

an abundant supply of fresh water and suitable food. The nystagmus time, weight, and pulse rate of each of the 14 birds were tested every other day during the period of medication. All measurements were made in the early afternoon and with the birds hooded in order to avoid any undue excitement from visual stimulation as well as to provide the most favorable conditions for the occurrence of post-rotation nystagmus. The pulse rate was obtained by listening to the bird's heart and tapping an automatic counter. The device used for rotation was electrically driven and operated in such a way as to insure absolutely uniform vestibular stimulation.

Throughout the entire period of the experiment both groups maintained an average body weight of approximately 14.5 ounces. However, by the third day of medication the average pulse rate of the experimental group had gone up to 186 beats per minute, while the control group remained around 160 beats per minute (which had been approximately the average rate of the experimental group during the preliminary testing period). With slight fluctuations these respective averages were maintained by the two groups during the remainder of the experiment.

Contrary to what might have been predicted, the average post-rotation nystagmus time for the two groups remained remarkably similar. On the original preliminary tests, each group had an average nystagmus time of about 18.0 seconds; at the termination of the experiment this average had dropped, due to the unavoidable effects of habituation (5), to around 12.0 seconds, but at no time was there a significant difference in the respective average nystagmus time of the two groups, although individual variations from time to time were quite marked.

These results would seem to indicate rather clearly that physiological variation in thyroid condition is not responsible for the observed fluctuations in the nystagmus time of pigeons. Whether the same is true of other species of birds as well as in the case of mammals, including man, will have to be determined by further investigation. Although this report leaves the problem of nystagmus-time variation still unsolved, the writers feel that the method employed may ultimately be successful and that the now very perplexing and apparently fortuitous fluctuations in nystagmus duration may, in time, become a very precise measure of some special organic condition.

SUMMARY

Although it has often been assumed that the duration of post-rotation nystagmus is normally invariable in a given individual and under objectively identical conditions of stimulation, it has been clearly demonstrated by various investigators that, on the contrary, this response is subject to decided and as yet unexplained fluctuations. Inasmuch as the duration of post-rotation nystagmus is supposed to depend on the sensitivity of the vestibular apparatus of the inner ear and since thyroid secretion is believed to have a positive effect on nervous irritability in general,

it seemed reasonable to infer that the observed and otherwise unaccountable variations in post-rotation nystagmus time might be due to corresponding changes in the thyroid condition of the subject. In order to test this inference, seven healthy adult pigeons were fed 1/20 gr. of desiccated thyroid gland twice a day for two weeks. A decided increase in the pulse rate was noted, but the average post-rotation nystagmus time of this group did not vary significantly from that of a control group of birds.

REFERENCES

1. Barlow, R. A.: The study of vestibular nerve function in myxedema. Am. J. M. Sc. **164**: 401. 1922.
2. Boenninghaus, G.: Ueber das Versagen der labyrinthogenen statischen Kompensation im affekt. Monatschr. f. Ohrenh. **60**: 1139. 1926.
3. Claude, H., H. Baruck and M. Aubrey: Les troubles vestibulaires dans la démence précoce catatonique. Compt. rend. Soc. de biol. **96**: 1376. 1927.
4. Detlefson, J. A.: The inheritance of acquired characters. Physiol. Rev. **5**: 244. 1925. Also, Are the effects of long-continued rotations inherited? Proc. Am. Philos. Soc. **57**: 292. 1923.
5. Fearing, F. S.: Post-rotational head nystagmus in adult pigeons. J. Comp. Psychol. **6**: 115. 1927.
6. Fenton, R. A.: Otolaryngologic aspects of commercial aviation. Ann. Otol. Rhin. & Laryng. **40**: 1070. 1931.
7. Güttich, A.: Beitrag zur Physiologie des Vestibularapparates. Beitr. z. Anat. Physiol., Path. u. Therap. d. Ohres. **7**: 1. 1914.
8. Hoshino, T.: Vestibuläre Reflexbewegungen des Auges beim normalen Kaninchen. Acta oto-laryng. **4**: 328. 1922.
9. Howell, W. H.: Text-book of Physiology. W. B. Sanders Co., Phila., 11th ed. 1930.
10. Jones, I. H. and L. Fisher: Equilibrium and Vertigo. J. B. Lippincott Co., Phila. 1918.

THE TREATMENT OF EARLY VOMITING OF PREGNANCY WITH SUPRARENAL CORTEX: CASE REPORTS

W. N. KEMP, B.A., M.D.
VANCOUVER, B. C.

The association of suprarenal cortical insufficiency with gastro-intestinal disturbances as shown by many recently reported laboratory experiments in dogs, coupled with the fact that the adrenal cortex hypertrophies in pregnancy suggested that the temporary and relative adrenal cortical insufficiency might be the etiological factor in the nausea and vomiting so common in the first trimester of pregnancy. It is assumed that the natural hypertrophy of the adrenal cortex incidental to pregnancy does not reach sufficient proportions to fully care for the mother's increased metabolic load until the end of the third month when the vomiting usually ceases. Six consecutive cases of the use of adrenal cortex material are herewith reported.

Case 1. Mrs. S. M. S. Age 34. Para. 2. Patient of Dr. M. Blair. Last menstruation, Nov. 20, 1931.

Past History—During her first pregnancy in 1928, the patient was very markedly nauseated *throughout* and vomited intermittently during the whole of the pregnant period. Her doctor resorted to many expedients without avail. Her labor apparently terminated in low forceps delivery and was otherwise quite normal.

Present Illness—She first consulted Dr. Blair on Jan. 8th, 1932. She complained of extreme nausea with vomiting occurring many times each day. She said that she felt exactly as she did during her first pregnancy. She was given suprarenal cortex (Armour) 9 grains a day. The first week showed little improvement; thereafter there was a cessation of nausea and vomiting. In her own words, "I never felt better." She continued symptom free until March 10th when she had the misfortune to abort.

Case 2. Mrs. J. Age 26. Para 1. Patient of Dr. T. H. Agnew. Last menstruation, Dec. 28, 1931.

Past History was irrelevant.

Present Illness—The patient consulted Dr. Agnew, Feb. 10th, 1932, for relief of nausea and vomiting. Different remedies were used without any amelioration in the condition. On Feb. 20th administration of suprarenal cortex (Armour) was started on a dosage of gr. 6 t. i. d. Within two days nausea and vomiting ceased. The dose was halved and the patient remained symptom free.

Case 3. Mrs. B. Age 27. Para. 1. Patient of Dr. Wm. Gunn. Last menstruation, Jan. 7th, 1932.

Past History was irrelevant.

Present Illness—This woman consulted Dr. Gunn on Feb. 11th complaining of nausea and vomiting. She had been vomiting several times a day and always "felt miserable." She was given 18 grains of suprarenal cortex (Armour) daily. At the end of three days nausea disappeared and vomiting ceased. She remained free of symptoms on gr. 3 t. i. d.

Case 4. Mrs. T. Age 27. Para. 3. Patient of Drs. J. L. Turnbull and W. B. Burnett. Last menstruation, October 27th, 1931.

Past History—This patient has two children aged 7 and 3 years. With the first pregnancy she suffered from the usual morning sickness. With the second

pregnancy she suffered from pernicious vomiting that necessitated hospitalization and intravenous gluco-saline therapy.

Present Illness—When she first consulted Dr. Turnbull on Dec. 18th the patient felt greatly nauseated and feared a return of the pernicious vomiting of the previous pregnancy. She was admitted to hospital for observation and necessary treatment. After consultation with Dr. Burnett she was given suprarenal cortex (Armour) in a daily dosage of 18 grains. Within two days she was free of nausea and up to date her pregnancy has been normal on a diminished dosage of Cortex.

Case 5. Mrs. B. Age 35. Para. 4. Patient of Dr. D. R. Shewan.

Past History—The patient has three children. Nausea and vomiting have increased in severity with each pregnancy.

Present Illness—She consulted her physician on Feb. 22nd for relief of nausea and vomiting. The last menstrual date was Jan. 15. The administration of the usual dosage of suprarenal cortex was of definite value in restoring her general well being and in controlling vomiting.

Case 6. Mrs. C. Age 28. Para. 2. Patient of Dr. Thos. Butters.

Past History was irrelevant.

Present Illness—On Jan. 15th, 1932, she consulted her doctor for the relief of excessive vomiting. She was found to be 6 weeks pregnant. Routine treatment had been of no use in controlling symptoms of excessive nausea and vomiting; suprarenal cortex (Armour) was prescribed in a daily dosage of 18 grains. There was no change in the patient's condition until the third day of treatment when nausea and vomiting definitely decreased and ceased entirely on the fourth day. The patient remained symptom free for two weeks when, on her doctor's instructions, she ceased to take her tablets of suprarenal cortex. Vomiting and nausea returned within two days to again disappear on the resumption of the medication. Financial difficulties forced her to cease treatment after two weeks. Nausea and vomiting returned but again ceased when the ingestion of the cortical tablets was resumed. After the end of the 14th week this patient was able to discontinue the medication without a return of vomiting.

DISCUSSION

The above reports are based upon the treatment of six consecutive cases of excessive vomiting during the first trimester of pregnancy. The psychic element is considered by some observers to be the most important factor in the causation of the vomiting of pregnancy. In the above series of cases no guarantee could be made to the patient as to the efficacy of the treatment. The fact that improvement did not take place for three or more days would lead one to think that the psychic element in the cure was negligible. Case No. 6 is a striking demonstration of the value of the suggested treatment in a phlegmatic patient.

The following cases are cited to show the possible value of suprarenal cortex and cortical extract liquid in the complications of the later months of pregnancy:

Case 7. Mrs. R. K. Age 22. Para. 1. Patient of Dr. M. Blair. Last menstruation, June 26, 1931.

Past History—The patient was a perfectly normal, healthy, athletic girl.

Present Illness—In the first trimester she was subject to the usual nausea and vomiting. Her systolic blood pressure ranged between 126 and 132 mm. Hg. with the diastolic from 70 to 80. Her urine remained normal. On Jan. 4th she complained that she had had very severe headaches for some days, had been nauseated and had vomited occasionally. She felt generally miserable. Blood pressure at this date was 140/80. The urine showed a trace of albumin. She was sent home to bed and given low protein and comparatively salt free diet together with suprarenal cortex (Armour) 9 grains per diem. After five days

treatment her headache disappeared, the urine became normal and blood pressure remained stationary at 140/80 during the remainder of the pregnancy. She was delivered normally the latter part of March.

Case 8. Mrs. S. Age 34. Para. 3. Patient of Dr. Anson Frost.

Past History—Both previous pregnancies had to be terminated at the seventh month on account of pernicious vomiting.

Present Illness—When the patient was seen with Dr. Frost on July 15, 1931, she was within one month of term. She had been in bed in hospital for six weeks on account of pernicious vomiting. She required daily intravenous infusions of 5 per cent glucose and could tolerate only a liquid or semi-solid diet. Her blood picture was that of a severe secondary anaemia. At this time she was given one cc. of liquid extract of suprarenal cortex (Armour) intravenously with no reaction of any kind. Twelve hours later she felt much better and was given another intravenous injection. She felt very markedly improved after the second injection and her appetite returned for the first time in 6 weeks. Unfortunately, she was allowed to satisfy her appetite to the fullest extent. The result was inevitable. She had a gastric upset and refused further suprarenal therapy. Labor was induced and she was delivered a few days later.

SUMMARY

1. The nausea and vomiting of the first trimester of pregnancy was treated with marked success by the oral administration of desiccated suprarenal cortex in six consecutive ambulatory patients.

2. Headache and albuminuria with a rising blood pressure was successfully treated in one case by the same therapy.

3. Pernicious vomiting was treated with temporary success in one case by the intravenous administration of liquid cortical extract (Armour).

Thanks are expressed to colleagues who collaborated in this treatment.

Abstract Department

The effect of hypotension on the secretion of an adrenal grafted into the neck (Influence de l'hypotension sur la sécrétion d'une surrénale greffée au cou). Bennati, D., J. Gautrelet and N. Halpern, Compt. rend. Soc. de biol. **104**: 752. 1930.

The adrenal of one dog was anastomosed into the carotid jugular circulation of another, whose adrenals had been removed. Hypotension produced by stimulating the vagus of the latter animal is followed by a secretion of adrenin from the graft which, of course, is without nervous connections.—J. C. D.

Vascularization of the human adrenal (Les pedicules vasculaires des glandes surrenales chez l'homme). Bleicher, M., Rev. franç. d'endocrinol. **8**: 385. 1930.

A description of the vascularization of the adrenal which may prove valuable in operative technique.—B. C.

Observations on adrenalectomy in marsupial hibernation and higher mammalian types. Britton, S. W., Am. J. Physiol. **99**: 9. 1931.

The results of adrenalectomy in the marmot and the opossum are not dissimilar from those observed in the cat. With the earliest appearance of symptoms of insufficiency, the blood sugar becomes significantly reduced and the blood non-protein nitrogen considerably increased. Muscular weakness in all types studied is then followed by convulsions (commonly) and eventually death ensues. Summer-operated groundhogs usually survive for 2 to 10 days following adrenal removal. Opossums may live for a few days to a few weeks after the operation. Death from adrenal insufficiency is inevitable although long delayed in winter-operated groundhogs. Such animals survive throughout the normal period of hibernation in apparent perfect health, although in common with their unoperated fellows they do not actually hibernate while in captivity. In early spring, death occurs with typical symptoms of adrenal insufficiency. The extended survival through the winter is attributed to the lowered metabolic demands during this season. Pancreatic and gastric mucosal lesions are common in groundhogs and opossums, similarly as in cats dying after exclusion of the adrenal glands.—Author's Summary.

Studies on the conditions of activity in endocrine organs. XXVII. Evidence that medulliadrenal secretion is not continuous. Cannon, W. B., Am. J. Physiol. **98**: 447. 1931.

Observations for and against the continuous secretion of adrenin are reviewed, and the point is made that the evidence in favor of continuous secretion has been obtained under disturbing experimental conditions. Records taken from quiet, healthy animals, with hearts denervated for some time and thereby especially sensitized to the action of adrenin, reveal no noteworthy difference between the basal heart rates before and after the adrenal medulla was inactivated, either by denervation or extirpation. Since the heart, even when freshly denervated, is, to a very high degree, sensitive to circulating adrenin, the conclusion is drawn that adrenin is not secreted continuously, but, as other experiments have shown, only in emergencies or for the preservation of homeostasis.—Author's Summary.

The effect of adrenalin and substances related to adrenalin (sympathol and ephetonin) upon the circulation (Über die Wirkung des Adrenalins und adrenalinverwandter Körper [Sympatol und Ephetonin] auf den Kreislauf). Hochrein, M. and J. Keller, Arch. f. exper. Path. u. Pharmakol. **156**: 37. 1930. Abst., Chem. Absts. **25**: 4045.

The cardiac and vascular effects of adrenalin, sympathol and ephetonin, involve several distinct factors. For 10-30 seconds, the right auricular and arterial pressures and the rate of arterial flow increases, owing to a mobilization of blood from the liver, spleen, etc. During this period the pressure in the vena cava below the renal veins is not affected. Following this period, the valves return toward normal. The secondary rise in blood pressure is accom-

panied by a decreased arterial flow, an increased rate of venous flow and an increased pressure in the right auricle, effects due to peripheral capillary contraction. In the coronary circulation this increased arterial pressure, coupled with a local vasodilatation, results in a greatly increased blood flow. The respiratory effect of these substances is not related in time to their effect upon arterial pressure. The adrenalin effect is very transitory, and is accompanied by cardiac irregularities and, in particular, predisposes to fibrillation. The ephetonin effect, although less marked, has the longest duration. It has the least contractile effect upon isolated vessels. Sympathol occupies an intermediate position as regards its stability and the duration and intensity of its pharmacological properties. Although it is more toxic, it does not have the undesirable side-effects upon cardiac conduction and rhythm. Therapeutically, it is indicated in diseases which cause a peripheral disturbance in circulation (acute infections, coronary thrombosis). It is used in place of cardiazole and as a supplement to digitalis and strophanthin in circulatory decompensation.

Studies on sympathol, a new adrenalin-like substance (Untersuchungen über Sympatol, einen adrenalinähnlichen Körper). Kuschinsky, G., Arch. f. exper. Path. u. Pharmakol. **156**: 290. 1930. Abst., Chem. Absts. **25**: 4047.

Sympathol is 60-100 times more effective as a vasopressor than adrenalin (using the l-sympathol, which is twice as active as the dl form, and 5 times as effective as d-sympathol). The substance is not affected by passage through the liver. It contracts peripheral vessels, but not as intensely as does adrenalin. Its pressor action becomes apparent even when it is injected into the small intestine, 3 times the intravenous dose being necessary to produce the same rise in blood pressure. Unlike adrenalin, its action is not decreased by ergotamine; but cocaine does cause an accentuation of its effect. On the heart-lung preparation, it causes a greater minute volume, a greater efficiency and amplitude of contraction and a greater frequency. It causes coronary dilatation, contraction of the renal vessels, and counteracts pilocarpine bronchospasm. Its action upon the intestine and uterus is similar to that of adrenalin. Unlike the latter, sympathol does not cause cardiac irregularities or an increase in auricular pressure. The lethal dose of l-sympathol for white mice is 0.7-0.8 mgm. per gram., of d-sympathol, 1.5 mgm. per gram, and of l-adrenaline 0.005 mgm. per gram, a 1:150 ratio in favor of l-sympathol. m-Sympathol is 4-5 times more active as a vasopressor than l-sympathol. In general, sympathol seems pharmacologically more like adrenalin than any of the other members of the group.

Endemic purpuric meningococcus bacteremia in early life. The diagnostic value of smears from the purpuric lesions. McLean, S. and J. Caffey, Am. J. Dis. Child. **42**: 1053. 1931.

Hemorrhage in the suprarenal gland was found in three cases of meningococcic bacteremia. In one case the hemorrhage was microscopic, while in the others it was extensive and bilateral with destruction of both adrenals. In the latter two the disease had a fulminating onset with marked prostration, cyanosis and early death within 19 and 36 hours, respectively, after the onset of known symptoms. In neither case were severe inflammatory reactions present in the cerebrospinal fluid. The adrenal damage may be the frequent cause of death in rapidly fatal cases. Those cases of shock which do not come to autopsy might be explained on a basis of suprarenal damage. The authors refer to others who have found adrenal hemorrhage in the fulminating type of cerebrospinal meningitis and call attention to the use of potent cortical extract in addition to epinephrine in this type of a case. Several of the cases in the series showed enlargement of the thymus and general lymphatic hyperplasia. The patients were all well nourished at the time of death. Westenhoffer claims that children with lymphatic constitutions are predisposed to meningococcus infection.—M. B. G.

Effect of extracts of the adrenal cortex on the survival of decapsulated guinea pigs (Influence des extraits cortico-surrénaux sur la survie du cobaye décapsulé). de Mira, F., J. Fontes and K. P. Jacobsohn, Compt. rend. Soc. de biol. **105**: 808. 1930.

Guinea pigs decapsulated and treated survived, on the average, 13 hours with the Hartman and Brownell extract, 13 hours with the Max Reiss extract, 16 hours with the Goldzieher extract, and with grafts, 25 hours.—J. C. D.

Coagulation time of the blood of adrenalectomized rats. Nice, L. B., O. C. Irwin and Ruth M. Kraft, Am. J. Physiol. **96**: 305. 1930.

Normal rats showed a well defined shortening in the rate of coagulation of their blood (averaging 47%) after being restrained and stimulated. The clotting time of the blood of the adrenalectomized rats after excitement was decreased in 15 determinations, increased in 5, while in one case the clotting time before and after stimulation was the same. The average decrease for the group as a whole was 13%. The results indicate that the adrenal glands are a large factor, but not the only one responsible for the shortening of the coagulation time of the blood of emotionally excited rats.—Authors' Summary.

On the adrenalin content in suprarenals and the amount of the adrenalin-like substance in the serum of guinea-pigs fed on a vitamin C free diet. Ohato, S., J. Biochem. **12**: 419. 1930. Abst., Physiol. Absts. **16**: 107.

The adrenalin content of the suprarenals and the amount of adrenalin-like substance in the serum of scorbutic guinea-pigs show subnormal values. Starvation also effects a lowering, but only of the serum adrenalin-like substance to the level of the scorbutic values.

The susceptibility of doubly suprarenalectomized rabbits to nicotine, histamine, ephedrine and typhoid vaccine. Oikawa, K., Tohoku J. Exper. Med. **18**: 27. 1931.

The sensitiveness of rabbits to nicotine, histamine, ephedrine, and typhoid vaccine (in 0.5% carbolic acid saline solution) was not wholly identical but only a little inferior to that of normal, when tested about two, three months or somewhat later after double suprarenalectomy.—R. G. H.

Studies on the lipolytic power of the adrenal gland (Etudes sur la puissance lipolytique des glandes surrénales). Parfentieff, I. and B. Sokoloff, Compt. rend. Soc. de biol. **107**: 114. 1931.

When tested on tributyrine, water extracts of whole bovine adrenal had no lipolytic action, nor any inhibitory action on lipase extracted from liver. —J. C. D.

The effect of total thyroidectomy on the structure of the pituitary gland in the rabbit. Bryant, A. R., Anat. Rec. **47**: 131. 1930.

Sixty-four to 110 days after extirpation of the thyroid gland in 5 rabbits (mostly young males) the hypophysis had increased from 1/7 to 1/3 over that of litter-mate controls. The increase is due to hypertrophy of the chromophobe cells of the anterior lobe. Some of these cells become vacuolated and ultimately degenerate. Acidophilic cells are less conspicuous and the basophilic are no longer in evidence in the experimental animals. These changes are interpreted as evidence of a depression in the secretory activity of the hypophysis as a result of the thyroidectomy.—A. T. R.

Studies on the conditions of activity in endocrine organs. XXVI. A hormone produced by sympathetic action on smooth muscle. Cannon, W. B., Z. M. Bacq and R. M. Moore, Am. J. Physiol. **96**: 392. 1931.

In a cat with heart denervated, adrenals and liver excluded from action and spinal cord severed in the mid-thoracic region (so as to permit, without anesthesia, painless operations in the hind part of the animal), stimulation of the sympathetic supply to the smooth muscle of the tail hairs (and of the blood vessels of the region) causes, for about two minutes, a gradual increase of blood pressure, a gradual increase of heart rate and a gradual increase of salivary secretion. The time relations of the increase and the slow return to the former state are, in each instance, similar to those reported for the denervated heart alone, in the previous paper, as a consequence of emotional excitement. If the blood flow into and from the legs and tails is hindered, the phenomenon is much reduced or is delayed until the flow is restored. Since the only tissue known to be affected by sympathetic stimulation at the base of the tail or on the mesenteric arteries is smooth muscle, since the only connection between the hind part of the animal and the responding denervated organs in

the fore part is the blood stream, and since interfering with the stream in the region where smooth muscle is stimulated either markedly depresses or abolishes the response, the inferences are drawn that a substance is given off from smooth muscle into the blood, that it is carried effectively by the blood to distant organs, and that it influences those organs in a favorable manner, i.e., as sympathetic impulses would influence them. Because the properties just mentioned are those of a hormone the substance given off by smooth muscle, when affected by sympathetic impulses, is regarded as a hormone. The substance arises not only from pilomotor muscles, but also from the smooth muscle of the intestine, and the bladder and uterus. Because the substance is derived from structures under sympathetic control, when they are influenced by sympathetic impulses, it is suggested that it be called sympathin. Sympathin is given off from the smooth muscle of the tail and can increase the heart rate after ergotamine has prevented sympathetic impulses from causing erection of the tail hairs. The bearing of these observations on those of Loewi and others on the humoral transmission of nerve impulses, the support which the observations bring to some early views of Elliott, and the possible relations of sympathin and adrenin, are considered in the discussion.—Authors' Summary.

Hormonal experimental catatonia. De Jong, H., Proc. Acad. Sc. Amsterdam, **34**: 576. 1931. Abst., Chem. Absts. **25**: 5205.

That dementia precox is due to an inner-secretory disturbance is assumed to gain support by these experiments. Adrenalin and acetylcholine in certain doses are shown to induce a symptom complex in higher animals, comparable to the motor phenomenon of human catatonia. Tyramine and hordenine cause no catatonic phenomena. With cats, 10 mgm. of adrenalin induces catalepsy, negativism, salivation, polypnea, etc. With one monkey, two 10 mgm. doses of adrenalin were fatal with hyperkinetic catatonic phenomena. With other monkeys smaller doses produced a restricted catatonic syndrome. With mice, thyroxin, pituitrin and menformone in large doses produced no detectable motility changes. Insulin causes hypermotility without cataleptic prestages. Five mgm. of acetylcholine chloride proved fatal for mice. Catatonic phenomena were obtained with ¼-⅛ mgm. With cats, 5 mgm. produced decided catalepsy and negativism with salivation and polypnea.

Unilateral castration and compensatory hypertrophy of the remaining testicle in cocks and ducks (Castration unilatérale et hypertrophie compensatrice du testicule restant chez le Coq et le Canard). Benoit, J., Compt. rend. Soc. de biol. **104**: 883. 1930.

The work is based on 10 cocks and an unspecified number of ducks. It was found that the removal of a testis from young cocks, young ducks, or from adult ducks, at the time when this gland is undergoing its normal periodic involution induces an hypertrophy of the remaining testis to a size equal to that of the two testes in control animals. This hypertrophy is due to an actual increase of testicular tissue and not to an increase in the diameter of the seminiferous tubules. This response does not occur in adult cocks or in drakes with active adult testes.—J. C. D.

Sex hormones and the sympathetic nervous system (Hormones sexuelles et système nerveus sympathique). Buchheim, W. and W. Zaleski, Compt. rend. Soc. de biol. **104**: 896. 1930.

Twenty female rabbits had small bits of uterus grafted into their ears. Later the superior cervical ganglion on one side was removed, thereby depriving the ear of its sympathetic supply. The graft responded to corpora lutea in the ovaries regardless of the sympathetic supply.—J. C. D.

Ovarian grafts in unspayed rats (Greffes d'ovaires chez des Rates entieres). del Castillo, E. B. and C. J. Calatroni, Compt. rend. Soc. de biol. **106**: 310. 1931.

Grafts into the kidney of female white rats took easily. They did not show mature ova though the immature were numerous. There was no effect demonstrable on the ovaries of the host.—J. C. D.

The influence of testis hormone upon the oestrous cycle in the rat. Ihrke, I. A. and F. D'Amour, Am. J. Physiol. **96**: 289. 1931.

Daily injection of testis hormone (prepared by Gallagher and Koch) into spayed female rats does not stimulate the cornified vaginal smear of oestrus or have any demonstrable effect. Injections of mixtures of testis hormone and oestrin into spayed females is accompanied by the cornified cell smear as long as injections are continued. When injections are stopped the leucocyte (or dioestrous) smear appears and is permanent. Testis hormone injected daily into normal females suppresses the oestrous cycle for the period of the injection. When injections are no longer given the normal cycle expressed by the vaginal smear reappears. Normal female rats with cycles suppressed by testis hormone give cornified smears within two to three days after injection of the sex stimulating anterior lobe secretion prepared from pregnancy urine.
—Authors' Summary.

Action of mammalian folliculin on the oviduct of turtles (Action de la folliculine de mammifère sur l'oviducte de la tortue). Kehl, R., Compt. rend. Soc. de biol. **105**: 512. 1930.

In young turtles (testudo iberica) five rat units of folliculin injected in two daily doses, produced a rapid development of the oviduct at the end of two weeks.—J. C. D.

Extraction, distribution and action of testicular hormones. Koch, F. C., J. A. M. A. **96**: 937. 1931. Abst., A. M. A.

Active preparations of a testis hormone have been concentrated to a fair degree of purity by Koch. The product acts best when injected subcutaneously or intramuscularly; the dose for action by mouth is at least ten times as high. The physiologic actions observed thus far are the effects on the secondary sex characters in capon and the accessory gonads in the mouse, rat and guinea-pig. No claim can be made that the product also affects behavior, metabolism or "vigor." Whether these responses are due to other hormones or whether larger doses over longer periods of treatment are involved remains to be determined. In the light of these results on animals, it is reasonable to expect that similar generalizations will hold with reference to man. Thus far there is no indication that this product can be of any value in restoring "vigor" to the aged or neurasthenic. However, if there is an indication for its use and if the dosage in man is comparable to that found in the capon, the daily injection for a 150-pound man would have to be an amount equivalent to at least 5 pounds of bulls' testes tissue or 2 gallons of normal male urine. If taken by mouth, the dose presumably would have to be much greater. These deductions, based on animal experimentation, indicate the probable fallacy of prescribing testis preparations to man. It must be recalled that most of the proprietary preparations now on the market are to be taken by mouth and that they simply are made up of the desiccated and defatted ram or bull testicles. In the defatting process, no doubt a considerable part of the trace of hormone originally present is removed and discarded. The recent report from this laboratory on a well-known proprietary product confirms these statements.

Effect of oestrin and lutein combinations on uterus of the mouse. Macht, D. I. and A. E. Stickels, Proc. Soc. Exper. Biol. & Med. **28**: 801. 1931.

A decided hypertrophy of the uteri of mature mice was found after the injection of oestrin alone, as indicated by the ratio of the uterine weight to the total body weight. When the same doses of oestrin were injected together with an extract of corpus luteum, no hypertrophy of the uterus occurred. The author suggests that the corpus luteum extract tends to counteract the hypertrophy producing effect of oestrin in mice. Similar results were obtained by feeding mice for periods of 2 to 5 weeks with preparations of oestrin and of corpus luteum.—M. O. L.

The action of testis hormone in correcting changes induced in the rat prostate and seminal vesicles by vitamine B deficiency or partial inanition. Moore, C. R. and L. T. Samuels, Am. J. Physiol. **96**: 278. 1931.

Testes of male rats upon a diet deficient in antineuritic fraction of vitamin B, or on insufficient diets containing an excess of B, were found to consist of normal seminiferous tubules in active spermatogenesis but the reproductive

accessories (prostate gland and seminal vesicles) were castrate in type. Daily injections of either testes hormone, or anterior hypophysis hormone from pregnancy urine, into animals with castrate accessories caused the castrate condition to be replaced by the normal state within a period of ten days. We interpret these findings in terms of a more general theory advanced elsewhere in the following manner: Partial starvation induced by diets deficient in vitamine B, or insufficient diets rich in B, leads to a poor nutritive state in the organism which affects the hypophysis. The inhibition of hypophyseal secretion leads to a lowered amount of the sex stimulating hormone available in the organism. In the absence of this stimulating substance the testes fail to continue their endocrine function and castrate accessories are present. Injections of testis hormone stimulate the accessories directly, whereas injections of hypophysis hormone stimulate the intact testes to secrete their hormone which then acts upon the accessories. There is evidence to show that under the conditions of the experiment the endocrine function of the testis is disturbed, whereas spermatogenetic function continues.—Authors' Summary.

Effect of diathermy on the basal metabolism as an indication of the hormonal activity of the testes in dogs (Influence de la diathermie sur le métabolisme basal, comme indice de la fonction hormonale des testicules chez les chiens).

Use of the diathermic reaction for the study of testicular insufficiency following resection of the ductus deferens (Emploi de la réaction diathermique pour l'appréciation de l'insuffisance testiculaire après résection du canal déférent). Ptaszek, L., Compt. rend. Soc. de biol. **104:** 1097; 1099. 1930.

The scrotum received diathermic treatment for 10 minutes. In normal adult dogs, the basal metabolism falls after this; in immature or castrated animals, it is unchanged; and in senile dogs, it rises. If both ducts are tied the reaction following diathermy changes in three months from the fall characteristic of testicular activity to the rise indicating a degenerated testis.
—J. C. D.

Studies on the uterus. V. The influence of the ovary on the motility of the non-gravid uterus of the unanesthetized rabbit. Reynolds, S. R. M., Am. J. Physiol. **97:** 706. 1931.

Marked uterine activity in the non-pregnant rabbit is associated with oestrus. Feeble activity has been twice seen in oestrus; moderate activity has been seen seven times. Anoestrus is usually associated with only feeble activity, or none at all. The motility of the uterus of a rabbit deprived of its ovaries during oestrus becomes irregular and progressively less in two to four days. Complete quiescence eventually supervenes. The change has been demonstrated in the same rabbit, by obtaining records both before and after castration. Replacement therapy in castrate rabbits with Theelin and Estrogen, commercial water and lipoid soluble oestrogenic extracts, may impart to the quiescent uterus of those animals, activity such as usually occurs in the presence of the ovaries during oestrus. Because of the conclusions noted in above, it is concluded that the ovary of the non-pregnant rabbit normally exerts a profound effect upon the motility of the uterus. Due to the occasional irregularities in uterine motility seen during oestrus, mentioned above, it appears that certain unknown extra-ovarian influences sometimes, though rarely, modify or completely annual the effect of the ovary on the motility of the uterus. The minimal effective dose of Theelin as administered is less than 2 rat units per kgm. body weight in recently castrated rabbits. Twenty rat units per kgm. is the minimal effective dose in rabbits ovariectomized for three weeks.—Author's Summary.

The composition and properties of milk from castrated cows. Staffe, A., A. Janoschek and W. Scheimpflug, Lait, **10:** 1087. 1930. Abst., Chem. Absts. **25:** 5457.

The quantity of milk given by castrated cows was greater than that given by normal cows. The content of total solids, fat and Cl was higher from the castrated cows. Lactose, albumin, globulin, casein, total nitrogen, the point of coagulation, coagulability by rennin and solids-not-fat differed only slightly in the milks from castrated and normal cows.

A study of the causes of the normal development of the mammary glands of albino rat. Turner, C. W. and A. B. Schultze, Missouri Agriculture Experiment Station Research Bulletin, **157**: 5. 1931.

Continuing a study of the hormones concerned in the development of the mammary gland and the initiation of milk secretion, there is reported a detailed anatomical study of the normal development of the gland of the albino rat. This is followed by studies of the influence of the estrus-producing hormone, corpus luteum extracts, and an extract from the anterior pituitary. It was found that small doses of the estrus-producing hormone produced only duct growth, while larger doses caused some lobule proliferation. Corpus luteum extracts alone caused no changes in the mammary gland of the albino rat. Corpus luteum extracts, when injected with large doses of the estrus-producing hormone (5 r. u. or more) produced lobule proliferation greater than that produced by the estrus-producing hormone alone; but not equal to that characteristic of a gland of a rat in advanced pregnancy. Thus far the extracts of the anterior pituitary of sheep have been ineffective.

—Authors' Abst.

The genital crisis of the new born produced by the ovarian sex hormone (La crise génitale des nouveau-nés, provoquée par l'hormone sexuelle ovarienne). Zaharescu-Karaman, N. and A. Nastase, Compt. rend. Soc. de biol. **107**: 396. 1931.

When tested on young girls injections of folliculin produced a vaginal hypersecretion and a transitory swelling of the mammary gland.—J. C. D.

Biological methods for diagnosing over- and under-activity of the anterior lobe of the hypophysis in man (Methode biologique de diagnostic des états d'hyperactivité et d'hypoactivité de la préhypophyse chez l'homme). Aron, M., Compt. rend. Soc. de biol. **105**: 585. 1930.

It is suggested that the very definite quantitative and qualitative response given by the guinea pig thyroid to the injection of normal urine would make a delicate test for normal activity of the hypophysis. Three daily doses of 15 cc. of whole urine were injected into young guinea pigs weighing about 200 grams. They were examined on the fourth day. The thyroid was about 40% overweight and showed histologically the picture of overactivity. The same results followed the injection of a single dose of 0.001 to 0.003 grams of fresh anterior lobe.—J. C. D.

Physiologic significance of the ovary stimulating hormone associated with extracts of the anterior lobe of the hypophysis (Signification physiologique du principe stimulant de l'ovaire, renfermé dans les extraits préhypophysaires). Aron, M., Compt. rend. Soc. de biol. **106**: 1046. 1931.

The evidence is by no means conclusive that the substance in the urine of pregnant women which stimulates the ovary is derived from the hypophysis.

—J. C. D.

Action of the anterior lobe of the hypophysis on the respiratory exchange and the glycogen in white rats (Action de lobe antérieur de l'hypophyse sur les échanges respiratoires et le glycogène du Rat blanc). Artundo, A. and P. Mazzocco, Compt. rend. Soc. de biol. **105**: 713. 1930.

White rats of 120 to 190 grams weight were injected intraperitoneally with fresh anterior lobes from rats. The respiratory exchange, the blood sugar and the glycogen of the liver and the muscles was not influenced by this treatment.—J. C. D.

The effects of extracts of the mammalian hypophysis upon immature salamanders. Burns, R. K., Jr., and A. Buyse, Anat. Rec. **51**: (No. 2). 1931.

Extracts of mammalian anterior hypophysis, administered to larval salamanders, produce effects on the reproductive system like those which follow homoplastic transplantation of hypophysis. The effects also resemble those which follow similar treatment in immature rats and mice. In male larvae, remarkable hypertrophy of the testis occurs, accompanied later by premature maturation phenomena. The activity of the testis also induces modifications of accessory structures. In some cases overstimulation results in degenerative changes in the testis. In females, growth of the ovary is relatively slight, but

many ovogonia enter the growth phase prematurely. This results in ovaries having many precociously maturing ovocytes, but a dearth of younger cells, with consequent limitation of size. Accessory parts are probably unaffected during the period of the experiment. The results are in keeping with the recent demonstration of an hypophysis-gonad ovulation mechanism in adult amphibians and with the fact that hypophysectomy is followed by regression of the reproductive system. The hypophysis-gonad-reproductive tract mechanism, in all its familiar aspects, prevails also in amphibians, and probably in vertebrates generally.—Authors' Abst.

Action of extracts of the anterior lobe of the hypophysis on the chemistry of the liver (Action des extraits hypophysaires antérieurs sur le chimisme hépatique). Cruz-Coke, E. and J. Altamirano, Compt. rend. Soc. de biol. **105**: 241. 1930.

In six rabbits, three receiving 1 cc. and the others 2 cc. of anterior lobe extract subcutaneously for eight days, there was an increase of water and of lipase in the liver.—J. C. D.

The effect of pituitary extract upon the tonus of the human pelvis and ureter and its possible application in the therapeutics of pyelitis and related conditions. Draper, W. B., W. Darley and J. L. Harvey, J. Urol. **26**: 1. 1931.

From a study of nine individuals it was found that pituitary extract and "pitressin" reduced the size and density of the pelvic and ureteral shadows. The reduction was proportional to the amount of drug injected and maximum 3 to 7 minutes afterward. Intravenous urography was used. Neither drug, as given intramuscularly interfered with diuresis produced by uroselectan. The reduction of the shadows is due probably therefore to accelerated drainage caused by active peristalsis of the pelvis and ureter. This was borne out by the relief given one case and suggests a possible line of treatment.—J. C. D.

Adiposogenital dystrophy, diabetes mellitus and albuminuria of neurogenic origin; two cases (Dystrophia adiposo-genitalis, Diabetes mellitus und Albuminurie). Ehrström, R., Acta med. Scandinav. **76**: 9. 1931.

Two cases of dystrophia adiposogenitalis associated with diabetes mellitus and albuminuria are reported. One occurred in a woman 55 years of age, in whom an hypophyseal tumor was diagnosed. For twelve years she suffered with diabetes and for one year with albuminuria. The second patient was a woman 26 years of age who, following her second childbirth, developed hypophyseal obesity, amenorrhea and genital hypoplasia. Both patients showed changes in the sella, choked discs, diabetes, changes in carbohydrate tolerance and insulin requirement. Both suffered from migraine, vasomotor disturbance and increase of blood pressure. Albumin finally appeared in the urine of both patients. The author considers that the albumin is of nervous or cerebral origin. The other symptoms could be traced to an irritating lesion in the subthalmic region caused by an hypophyseal affection. The resulting vasomotor disturbances he considers responsible for the renal symptoms, migraine and hypertension.—H. G. Beck.

Relation of Prolan to the anterior hypophyseal hormones. Evans, H. M., K. Meyer and Miriam E. Simpson, Proc. Soc. Exper. Biol. & Med. **28**: 845. 1931.

A Prolan preparation which when given alone produced a maximal effect in young animals, that is ovaries weighing about 60 mgm., was given in combination with anterior lobe extract containing both growth and gonad stimulating properties. This extract, in the doses used, when given alone either failed or barely provoked sexual maturity at the end of the 100-hour period. The mixture of this extract and Prolan had a remarkable effect in producing ovaries weighing an average of 156 mgm., and filled with corpora lutea and large follicles. Hypophyseal extracts rich in the gonad stimulating hormone and lacking the growth principle could not be activated by Prolan, but growth hormone preparation free from gonad-stimulating properties were typically activated. The authors postulate that Prolan either converts an inactive prohormone in the hypophysis into an active form or else is able to convert the growth hormone into the gonad stimulating one.—M. O. L.

The effect of anterior hypophyseal implants upon senile ovaries of mice. Hoffman, J., Am. J. Obst. & Gynec. **22**: 231. 1931.

In 20 experiments it was found that the ovaries of old, sexually degenerated mice may be used as test objects for the effect of anterior hypophyseal implants. These implants seem to be capable not only of initiating ovarian function in immature mice, but also of re-establishing ovarian activity in old, menopausal mice. Hypophyseal implants apparently possess distinct stimulating properties by reason of the hormone which they contain: they do not continue to grow and produce additional hormones, but their effect upon the activity of the ovary seems to be continued even after their own activity has ceased. It is suggested by these experiments that old, nonestrus mice, when once stimulated, can be kept sexually active for a considerable time without further stimulation. The anterior hypophyseal implants may act by mobilizing the latent, residual hormones of the senile ovaries. In one of the experimental animals, ovulation was restored and succeeded by the gravid state.
—Author's Summary.

Pigmentary effector system. VI. The dual character of endocrine coördination in amphibian color change. Hogben, L. and L. Slome, Proc. Roy. Soc., London, **108**: 10. 1931. Abst., Chem. Absts. **25**: 4317.

The dermal melanophores of Xenopus laevis are subject to a dual endocrine control, in which the pituitary secretion is one factor, while the other factor possibly is associated with the pars tuberalis of that gland.

Note on the coagulation properties of the posterior lobe of the hypophysis (A propos de l'action hypercoagulante des extraits rétrohypophysaires). La Barre, Jean and A. Patalano, Compt. rend. Soc. de biol. **105**: 472. 1930.

Blood serum plus "Cytozyme" was tested for coagulation time with pituitrin, vasopressin extract and oxytocic extract. The two latter had no effect while pituitrin perceptibly reduced the time.—J. C. D.

Effect of castration, grafts and implantation of the gonads on the anterior lobe of the hypophysis (Influence de la castration, des greffes et des implantations de gonades sur le lobe antérieur de l'hypophyse). Martins, T. and A. Rocha, Compt. rend. Soc. de biol. **105**: 793. 1930.

In rats gonadectomy is followed within ten days by the appearance of "cells of castration" in the anterior lobe of the pituitary. These disappear after ovarian grafting but not after testicular grafting in the female. In the male testicular implantation and injections restore the hypophysis without restoring the atrophied genital tract, but ovarian grafts are ineffective.
—J. C. D.

Collection of illustrative cases of hypophyseal infantilism (Zur Kasuistik des hypophysären Infantilismus). Popoff, H., Endokrinologie, **9**: 195. 1931.

After referring to the divergent experiences of others with anterior pituitary preparations, the author reports a case of infantilism with marked retardation of sexual development in a boy of 18 years, who had the appearance of an 8-10 year-old lad. He was treated with raw hypophysis orally, grew 12½ cms. in a year and developed normal genitalia and secondary sex characteristics. Pubic and axillary hair and mustache grew properly, voice changed to adult pitch, and the patient's character changed; he became cheerful and vigorous and manly feelings were aroused.—H. Lisser.

Ineffectiveness of Prolan in hypophysectomized animals. Reichert, F. L., R. I. Pencharz, Miriam E. Simpson, K. Meyer and H. M. Evans, Proc. Soc. Exper. Biol. & Med. **28**: 843. 1931.

In a completely hypophysectomized female dog about 8 months old, the daily administration of 30 cc. of Prolan for 53 days was ineffective in preventing infantilism of the genitalia. After a rest period another course of treatment for a month with Prolan had no effect on the condition of infantilism. In two other hypophysectomized dogs, and in one hypophysectomized female cat Prolan of proven potency was unable to re-establish the normal development and function of the reproductive system.—M. O. L.

Studies on the physiology of reproduction in birds. XXXI. Effects of anterior pituitary hormones on gonads and other organ weights in the pigeon. Riddle, O and Irene Polhemus, Am. J. Physiol. **98**: 121. 1931.

Tests were made of the effects of various pituitary hormones on weights of gonads and several other organs in 57 birds; 39 blank-injected birds were used as controls. The immature testis of the dove and pigeon provides an extraordinarily sensitive test for the sex maturity hormone; 10 daily doses yield weight increases of from 500 to 2200%; 3 daily doses give increases of more than 100%. The growth response of the ovary of the immature dove and pigeon is not more than one-third or one-fourth that observed in the testis. Alkaline extracts of the anterior pituitary which were rich in the maturity principle, and probably contained the growth hormone, produced prompt and marked increase of weight in thyroid and liver; most other organs showed little or no change in size. Antuitrin is capable of stimulating growth in the immature testes; but in similar dosage and short-term tests it gives no measurable response in the ovaries. None of these results is ascribable to contamination of the extracts by posterior lobe principles; under the conditions observed in these tests pitocin and pitressin do not affect the size of gonads, thyroids or liver. The luteinizing hormone from pregnant urine has no effect on size of liver or thyroid, but it decreases the size of the oviduct (uterus) and stops or retards growth in the ovary. Its action is distinct from, perhaps antagonistic to, that of the maturity principle.—Authors' Summary.

The relation of the anterior pituitary hormones to the development and secretion of the mammary gland. Turner, C. W. and W. U. Gardner, Missouri Agriculture Experiment Station Research Bulletin, **158**: 5. 1931.

Moderate doses of estrus-producing hormone obtained from the urine of pregnant cattle when administered daily over a period of 21 days produced no significant changes on the mammary glands of mature rabbits. Large amounts (400 rat units) of estrus-producing hormone obtained from the urine of pregnant cows and the corpus luteum extract produced a slight secretion of milk when simultaneously administered. The assumption has been made that this lactation was due largely to the estrus-producing hormone which in large amounts may activate the pituitary. Pseudo-pregnancy may be produced in the rabbit by intravenous injections of extracts containing too small an amount of gonad-stimulating hormone to be effective when subcutaneously administered. Pseudo-pregnancy thus induces the characteristic development of the mammary glands. The mammary glands of mature castrated female rabbits have been stimulated to secretory activity by an alkaline extract obtained from sheep's anterior pituitary. The lactation was equal to that occurring following parturition. The degree of involution of the mammary glands of the mature castrated female rabbits did not in any way alter the effect produced by the alkaline extract. A great variation in the size of the alveoli of the glands of the experimental animals was observed. The larger alveoli were found in the proliferated glands of rabbits whose control glands had shown the existence of but a small amount of lobular tissue. From the results of the experiment it appears that the stimulating substance is effective only in the activation of the secretory cells of the alveoli. It appears that the initiation of milk secretion is due to a definite "lactation-producing" hormone secreted in the pituitary as has been suggested by Stricker and Grüter (1929) and Corner (1930).—Authors' Summary.

Spontaneous hypophyseal hypoglycemia (Ein neues hypophysäres Krankheitsbild: Die hypophysäre Spontanhypoglykämie). Wilder, J., Deutsche Ztschr. f. Nervenh. **112**: 192. 1930. Abst., Physiol. Absts. **15**: 190.

Two cases are presented, both of which showed clinical signs and symptoms of hypophyseal disease. In both cases there were spontaneous attacks of hypoglycemia accompanied by varying, transitory, psychical, and neurological symptoms. The author discusses in detail the psychical and neurological symptoms of hypoglycaemia, and also briefly reviews the literature on the relation of the hypophysis to sugar metabolism.

Studies on the hypotensive action of insulin free pancreatic extracts (Recherches sur l'effet hypotenseur des extraits pancréatiques désinsulinisés). Alessandri, H., Compt. rend. Soc. de biol. **105**: 247. 1930.

Gley and Kisthinios have claimed the existence of a separate hypotensive hormone in the pancreas. In rabbits results similar to theirs are given by extracts of the brain or liver. Histamine, choline or peptones may be responsible. In man an injection of acetylcholine gives similar results.—J. C. D.

The action of insulin on the frog; influence of dosage, temperature excision of liver, administration of glucose, sodium bicarbonate and calcium gluconate on reaction of frog to insulin. Barlow, O. W., W. N. Vigor and R. I. Peck, J. Pharmacol. & Exper. Therap. **41**: 229. 1931.

Insulin produces, consecutively, two distinct types of convulsions in the frog. These effects are due to stimulation of the medulla and spinal cord. The time of development, as well as the nature of the reactions, is closely related to the dosage administered. The initial reaction occurs 3 to 90 minutes after the injection of 0.5 to 2 units of insulin per gram of frog and is characterized by fibrillary twitches or clonic convulsions. This stage passes off gradually and is succeeded by depression. The terminal or extensor convulsions are grossly comparable to those of strychnin or late morphine poisoning and occur 40 to 96 hours after the injection of insulin. Elevation of temperature potentiates the toxic and convulsive effects of insulin. The nervous system and carbohydrate metabolism react independently to insulin. The initial convulsions seem to occur at a period when the blood sugar level is 100 to 600% above normal. The terminal extensor convulsions are accompanied by a mild subnormal blood sugar level but this edema and hydrema present, probably contributes to the hypoglycemic level. The significance is open to question as sugar values of equal magnitude occur without insulin. The administration of $NaHCO_3$ or calcium gluconate does not significantly influence the reactions of the frog to insulin. Excision of the liver did not affect the convulsant reaction but definitely shortened the survival period usually noted in hepatectomized controls without insulin. This study does not establish whether the beneficial action of the liver is due to its value as a glycogen store or to its function as a detoxifying mechanism. However, the administration of dextrose was without effect on the duration of the survival period after insulin.
—O. W. Barlow.

Insulin and heart rate after sympathectomy and vagotomy. Dworkin, S., Am. J. Physiol. **96**: 311. 1931.

The action upon the heart rate of hypoglycemia-inducing doses of insulin was tested in normal cats, and in cats surviving excision of portions of the autonomic nervous system. The following changes may occur: (1) Acceleration, due to central sympathico-adrenal impulses; (2) Slowing, due to central vagus stimulation; (3) Slowing, due to a peripheral action. In the intact animal these effects are expressed in a heart rate that is seldom above the basal level. The inference is that, while both divisions of the autonomic nervous system may be stimulated during insulin hypoglycemia, it is the vagus influence that predominates in organs that are innervated by both sets of nerves. These observations are in accordance with the findings of Bulatao and Carlson and correlate them with the work of Cannon, McIver and Bliss. Conclusions very similar to these, regarding the action of insulin upon the gastrointestinal tract, have been arrived at by Quigley and Templeton. Insulin has a delayed action upon the heart rate, in completely sympathectomized cats with heart denervated, manifest in a prolonged, though not marked slowing. This slowing develops gradually, attaining the maximum long after the lowest blood-sugar level has been reached, and some time after injection of glucose. Injected without previous insulin administration, glucose has no definite effect on heart rate in these animals. The slowing can be promptly abolished by atropine sulphate.—Author's Summary.

A clinical and anatomic contribution to the knowledge of combined diabetes mellitus and insipidus; report of a case treated with insulin and salyrgan in which the patient died with symptoms of hypoglycemia. Gellerstedt, N. and C. Grill, Acta med. Scandinav. **75**: 586. 1931.

The authors describe a case of diabetes mellitus-insipidus, treated with insulin and salyrgan (a diuretic mercury compound), in which death ensued in

hypoglycemic coma, and the pancreas was without remarkable histological changes, but the hypophysis showed a peculiar heteromorphous composition of the cyst colloid of the pars intermedia as well as rarefaction of the colloid appearing as free droplets. Further serious nephrotic changes were found in the kidneys. On the strength of the evidence of current literature as regards diabetes mellitus-insipidus as well as the anatomical facts of diabetes mellitus and the special result of autopsy in the case described above, the authors assume that a primary disturbance of the hypophysis may have been the cause of the complicated metabolic disease. As regards the effect of salyrgan in diabetes insipidus, stress is laid on the relation between the diminished excretion of urine and the kidney changes observed. To explain the patient's death in hypoglycemic coma in spite of there being ample amounts of glycogen in the liver, the authors assume that in this case there must have existed an increased susceptibility to insulin, possibly connected with the changes of the hypophysis. In corroboration of this they refer to the fact that in animals deprived of their hypophysis, susceptibility to insulin is much increased. In cases of diabetes mellitus in which there is reason to suspect an injury of some kind to the hypophysis, the practical consequence should therefore be the use of the greatest possible caution as regards insulin administration. Starting from a critical examination of the investigations into the significance of the hypophysis colloid the authors arrive at this opinion: It cannot be considered to have been conclusively proved that the substance mentioned plays no role in internal secretion. On the contrary, the authors are inclined to think that, in the case described, the morphological change of the hypophyseal colloid may be the result of an organic dysfunction that can be associated with the metabolic disease of the patient. Since, unfortunately, an examination of the mesencephalon was not made, the assumption is made with reservation.
—Authors' Summary.

Use of insulin in vagotonia and sensitization to insulin (Emploi de l'insuline dans les etats vagotoniques et sensibilisation a l'insuline). Joltrain, Rev. franç. d'endocrinol. **9**: 53. 1931.

Injections of insulin in a number of vagatonic conditions and colloidoclastic symptoms, particularly in urticaria and asthma have furnished unsatisfactory results. The author describes an asthmatic crisis in the case of a chemist who was progressively sensitized to insulin, and draws attention to undesirable results which may follow the use of insulin. In this regard he notes toxic conditions simulating pseudo-bulbar manifestation in a tubercular diabetic receiving intensive insulin therapy.—J. Gagnon.

Effect of insulin and epinephrine on the sugar content of the cerebrospinal fluid. Lukacs, J., Magyar orvosi arch. **30**: 591. 1930. Abst., Chem. Absts. **25**: 2488.

The sugar of the spinal fluid is decreased after the injection of insulin. Decrease in blood sugar sets in sooner than that in spinal fluid. Preceding the decrease in the sugar of the spinal fluid a temporary increase takes place; this is not true for blood sugar. Adrenalin raises the sugar in the spinal fluid and also in the blood; however, the increase in blood sugar takes place first.

Insulin in malnutrition. Metz, R. D., J. A. M. A. **96**: 1456. 1931. Abst., A. M. A.

In the treatment of malnutrition the authors order the usual general diet and inject insulin 30 minutes before each meal. On the first day, 3 doses of 10 units each are given. This is increased 5 units each day up to 20 or 30 units 3 times daily. They have found 20 units 3 times daily most satisfactory. They have had no experience with its ambulatory usage. The insulin reaction, naturally guarded against by the tissue sugar, is an important consideration. It is to be explained minutely and emphatically to all patients who receive insulin. This should be done at the beginning of the treatment. It is really preferable to cause a hypoglycemia and explain fully the symptoms as they arise. The pulse first becomes rapid and the vision blurred with mydriasis. Then follows the nervousness best illustrated by the increasing tremor of the extended fingers. Then ensues hunger, which becomes more and more intense. Then appears perspiration with its subsequent thirst and weakness. These symptoms are important to the patient in inverse proportion to the stability of the nervous system. Patients should not be allowed to show greater evidence of

hypoglycemic state, the patient takes a recurrence as a matter of course, calmly and without excitement. To give the patient a more profound sense of security, sucrose is kept on the bedside table so that it is easily accessible at all times. As an additional precaution, orange juice and commercial grape juice are readily available. As a supplement to these, a tray is in readiness on which are placed all necessary apparatus and materials for intrvenous injection of 20 and 50% dextrose in varying quantities. These precautions practically obviate any serious calamity that might be inaugurated. When the weight has reached a definite maximum, insulin loses its influence. This maximum is closely governed by the particular individual's normal weight. Among the beneficial effects of this treatment, the gain in weight is of primary importance, although the general improvement frequently surpasses it. This seems to be the result of a readjusted metabolism. Whether this is brought about in the constitutionally asthenic person purely through an endocrine readjustment is, as yet, speculative. Nevertheless, its general effects are quite obvious. Five unselected cases are reported to illustrate the possibilities of the treatment of malnutrition with insulin.

The effect of the ingestion of burdock root on normal and diabetic individuals. A preliminary report. Silver, A. A. and J. C. Krantz, Jr., Ann. Int. Med. **5**: 274. 1931.

The dried root of the burdock was powdered and extracted with ethereal solvents. By exposing the powder to low heat and later re-extracting with an acetone-alcohol mixture, the fat and bitters were removed. This powder contained about 60% of digestible carbohydrate, the remainder being mainly cellulose. This powder with butter, water, salt, saccharin and a few drops of ginger was made into cookies. The carbohydrate from 54-81 grams of burdock was absorbed and utilized. Mild diabetics can be kept aglucosuric by the administration of burdock root.—E. L.

A case of diabetes mellitus and fatty diarrhea due to carcinoma of the pancreas. Treatment with very high carbohydrate diet and insulin. Urmy, T. V., C. M. Jones and Josephine C. Wood, Am. J. M. Sc. **182**: 662. 1931.

A case is reported of colloid adenocarcinoma of the pancreas of probably 4 years and possibly longer duration. During the last 4 years of his life the patient tolerated well a cholecystogastrostomy done to relieve biliary obstruction. During the last year and a half, he was known to have mild diabetes, and during the last year he exhibited the classic picture of external pancreatic insufficiency. The emaciation and general debility produced by all three of these factors, carcinoma, pancreatogenous fatty diarrhea, and diabetes, were extremely well combated by treatment with a very high-carbohydrate diet plus insulin. Adequate digestion and absorption from the intestine were maintained, the utilization of carbohydrate foods was vastly improved, and there was a marked resultant increase in weight and strength. The general effects of the carcinoma were successfully resisted, although its pain, never severe, persisted and hemorrhage and infection secondary to the tumor finally led to rapid death. From this case we are able to conclude, in agreement with other observers, that a high-carbohydrate intake is by far the most advantageous type of diet in external pancreatic insufficiency. Enzyme preparations, if not valueless, may be entirely unnecessary. The use of insulin is to be recommended not only for its aid in the prevention of glycosuria, but also for what general metabolic effect it has in the production of weight increase. High-carbohydrate-low-fat diet with insulin enhances rather than impairs carbohydrate tolerance. We have been unable to demonstrate that diabetes produced by encroachment of tumor tissue on the pancreas differs clinically in any other way than in degree from so-calld "true" diabetes.

—Authors' Summary.

The percentage of eosinophils in blood smears from insulin-treated diabetics. Watson, E. M., Am. J. M. Sc. **182**: 231. 1931.

Eosinophilia is not a generally occurring incident in diabetics receiving insulin treatment. Its presence in some cases must be admitted. Seventy differential blood counts from 43 diabetics receiving insulin revealed a definite eosinophilia in only 1 case. This low incidence of eosinophilia under such conditions is not in accord with the findings of previous investigators. No explanation is offered for the discrepancy in the results. The average percentage of

eosinophils in 43 diabetics receiving insulin was not appreciably different from the average percentage of eosinophils in 20 diabetics who were treated by diet alone without insulin.—Author's Summary.

The insulin coefficient, an improved method for the clinical control of diabetes mellitus. Williams, J. R., Ann. Int. Med. **5**: 264. 1931.

The author believes that the present criteria for the diagnosis of diabetes (high blood sugar, glycosuria and abnormal reaction to glucose tolerance test) are not satisfactory. The reasons advanced are: (1) The marked variations in blood sugar, since they depend upon the insulin concentration or activity at the time of procuring the specimen. (2) The qualitative tests of the urine with copper solutions are questioned because of the probable presence of other reducing substances than glucose. The chief action of insulin is the formation of glycogen from dextrose. The author has found that in the uncomplicated, well-controlled diabetic, one unit of insulin promotes the utilization of four grams of glucose. The insulin coefficient is defined as the maximum amount of insulin which a patient can produce in twenty-four hours. The following classifications using this method have been made: Normal individual, 100 plus; borderline diabetic, 75 minus; mild diabetic, 40-75; moderately severe 25-40, and severe, 20 or less. In treatment, the coefficient is determined by a careful study for several days. Insulin reactions are a sure sign of wasted insulin.
—E. L.

Parathyroidectomy and vitamin D. Influence on the blood calcium (Parathyroïdectomie et vitamine D. Influence sur le calcium sanguin). Arthus, A. and A. Jedrzejowska, Compt. rend. Soc. de biol. **107**: 105. 1931.

Rabbits were fed a vitamin D containing substance, vigantol. This was fed only after the operation in some cases and only before in others. In proper doses at either time it enables the animals to survive without evident symptoms. Vigantol does not prevent a fall in blood calcium after parathyroidectomy but does prevent the reduction reaching the danger point.—J. C. D.

Complete thyro-parathyroidectomy and cardiac-moderation (Thyroparathyrïdectomie totale et cardio-modération). Arthus, A., Compt. rend. Soc. de biol. **107**: 107. 1931.

Rabbits were fed vitamin D which protects them from parathyroidectomy and the effects of various procedures on the heart rate were followed. The operation did not affect the sensitivity of the neuro-cardiac mechanism.
—J. C. D.

Studies on thyroglobulin. I. The digestibility of thyroglobulin. Barnes, B. O., A. J. Carlson and A. M. Riskin, Am. J. Physiol. **98**: 86. 1931.

Quantitative studies are reported which show that thyroglobulin is easily digested in vitro by pepsin and trypsin. The Sorensen formol titration shows a steady increase in the carboxyl groups. Precipitation reactions with ammonium sulfate show that the iodine containing protein is being digested. Analysis of the gastro-intestinal tract during normal digestion indicates that thyroglobulin is digested in a normal manner. None of the iodine in the blood during digestion of thyroglobulin is precipiated by half-saturated ammonium sulfate.—Authors' Summary.

A contribution to the understanding of the function of the thyroid gland and iodine metabolism in pregnancy (Beitrage zur Kenntnis der Schilddrüsenfunktion und des Jodstoffwechsels in der Gestation). Bokelmann, O. and W. Scheringer, Arch. f. Gynäk. **143**: 512. 1931. Abst., Chem. Absts. **25**: 5197.

In pregnancy the iodine content of the blood is relatively high from the second or third month, increases rapidly until the seventh month, remains at the same height until the ninth month, falls slightly in the last month of pregnancy and very gradually falls after delivery, not reaching the normal level for some weeks. No relation was made out between the height of concentration of iodine in the blood and either basal metabolism or carbohydrate assimilation. The increase in size of the thyroid gland noted early in pregnancy is an expression of a physiologic increase of activity and increased storage of the iodine containing secretion. The increase in endogenous iodine metabolism is

followed by an increased concentration of iodine in the blood. The cause of the increased activity of the thyroid gland in pregnancy may lie in a hypertonus of the vegetative nervous system.

Aberrant thyroid. Cattell, R. B., J. A. M. A. **97**: 1761. 1931. Abst., A. M. A.

The author reviews 13 cases of lateral aberrant thyroid. All showed a similar structure of papillary cystadenoma. In considering this group of cervical tumors, the author points out the low grade of malignancy as compared with other epithelial tumors involving the cervical glands. These tumors frequently go unrecognized and may be reported as metastatic carcinoma of unknown origin in the cervical glands. It is believed that neck tumors, outside of the thyroid gland showing papillary cystadenoma, are of lateral aberrant thyroid origin and are the result of arrested development. Satisfactory results were obtained by radical removal followed by postoperative irradiation. It is important to recognize them, since a good prognosis can be given.

Clinical aspects of thyroid malignancy. Clute, H. M., New England J. Med. **205**: 1083. 1931.

In a series of 6,535 patients suffering from thyroid disorders 3% had tumors which were malignant as proved by histological and clinical evidence. The author gives the following summary of his study of this series: "Since 90% of thyroid malignancy arises on the basis of a pre-existing adenoma, this must be considered as the outstanding premalignant lesion in the thyroid. There are relatively few clinical findings by which an early malignant degeneration in a thyroid adenoma can be distinguished. Marked firmness and fixation of the adenoma are very suggestive of malignant changes. When a thyroid adenoma is removed and is found to show malignancy on histologic examination, postoperative x-ray therapy is desirable, and, we believe, has a distinct value. If no recurrence of the malignancy occurs within a year of the time of removal of the tumor, our experience goes to show that recurrence need not be expected at a later date. The most serious types of thyroid malignancy are those which arise as a diffuse, rapidly spreading process in the thyroid gland and which are in many instances unrelated to the presence of any adenoma in the gland. In such cases there is a rapidly growing tumor, which early metastasizes to the adjacent lymph glands and to the lungs, and which is readily diagnosed on clinical examination as malignant because of its stony hardness, its fixation and its interference with breathing and swallowing. Surgery and x-ray treatment are of relatively slight avail under these conditions and the disease is rapidly progressive to a fatal termination.—J. C. D.

Action of thyroxin on the sodium chloride equilibrium of the blood (Action de la thyroxine sur l'équilibre chloresodium du sang). Coelho, E. and C. Oliveira, Compt. rend. Soc. de biol. **105**: 801. 1930.

In six out of eight subjects who received 2 to 4 cc. of thyroxin there was a reduction of chlorine in both the blood cells and plasma half an hour after the injection.—J. C. D.

Factors affecting size and iodine content of the thyroid in fowls. Cruickshank, Ethel M., Proc. Fourth World's Poultry Congress, P. 237. 1930. Abst., Chem. Absts. **25**: 4303.

The iodine content of the thyroid is affected by ingestion of food, age, species and season. In the pullet the maximum percentage was not reached until 25 to 30 weeks. The seasonal variation in thyroid weight was from 0.085 gr. in March to July to 0.13 gr. from January to March, with the greatest weight previous to the period of maximum egg production. It is probable that seasonal variation is related to egg production since the ovarian tissue contained merely a trace, the small ova very small amounts and the mature yolk appreciable amounts of iodine.

Variations in glycogen content of the heart in animals with experimental hyperthyroidism (Sur les variations du glycogène cardiaque chez l'animal en hyperthyroïdie expérimentale). Defauw, J., Compt. rend. Soc. de biol. **105**: 228. 1930.

In rats and rabbits fed or injected with thyroid over periods up to 10 days the glycogen of the heart is much reduced.—J. C. D.

The influence of hypnotics and thyroxin on diuresis (I. Über die Beeinflussung der Thyroxindiurese durch Schlafmittel und andere Pharmaka. II. Über Unterschiede der Diurese nach peroraler und intravenose Flüssigkeitszufuhr und ihrer Änderung durch Schlafmittel). Epstein, E. Z., Arch. f. exper. Path. u. Pharmakol. **142:** 214. 1929. Abst., Physiol. Absts. **16:** 67.

The diuresis produced in rabbits by giving 50 cc. of water by mouth is much increased if 1.0 mgm. of thyroxin is injected subcutaneously at the same time. This effect is inhibited by the subcutaneous injection of pituitary extract, ergotamine, or hypertonic glucose solution. The effect was not obtained if thyroxin was injected after the intravenous injection of physiological saline. When the liquid was given in this way the slight diuresis obtained was increased by paraldehyde, luminal, and iso-butyl-allyl-barbituric acid. It is argued that the effects of these drugs cannot be on the kidney tissue itself.

Persistence of an embryonic structure in the thyroid of the adult hedge hog (Persistance d'une structure embryonnaire dans le corps thyroïde du Hérisson adulte). Florentin, P., Compt. rend. Soc. de biol. **105:** 591. 1930.

In a ten months old male hedge hog the thyroid showed histologically two zones. The outer one shows the classic picture of colloid filled follicles. The inner zone is made up of anastomosing tubules whose lining cells give a reaction for mucus. These are evidently derivatives of the thyroglossal duct. The arrangements support the theory that the thyroid is derived from what was originally a mucous gland.—J. C. D.

The cardiac output in hyperthyroidism. Fullerton, C. W., Johns Hopkins Hospital Bull. **46:** 203. 1930.

A parallelism is to be found between the increase in the basal metabolism and the cardiac output per minute in hyperthyroidism when the cardiac output is measured under basal conditions. Only slight damages are found in the blood pressure patients with hyperthyroidism before and after treatment. It is therefore probable that the increase in cardiac output per minute is an approximate numerical measure of the increased work of the heart in this condition. The fairly close relation which exists between elevation of metabolism and cardiac output in hyperthyroidism strongly suggests that the level of the metabolism in the decrease is a factor of the first importance in the regulation of the cardiac output per minute under basal condition.

—Author's Summary.

The treatment of Basedow's disease with myxedematous goiter (Essai de traitment de la maladie de Basedow par un extrait de goître myxoedémateux). Jaquerod, Rev. franç. d'endocrinol. **8:** 407. 1930.

Four cases of Basedow's disease showed rapid improvement when treated with myxedematous thyroid gland from a human source. Necessary precautions are suggested.—B. C.

Rare ocular changes in thyroidal disturbances (Ueber eine seltene Augenveränderung bei Schilddrüsenstörungen). Gasteiger, H., Wien. klin. Wchnschr. **44:** 887. 1931. Abst., J. A. M. A. **97:** 1042.

Gasteiger reports the case of a man, aged 47, who developed symptoms of exophthalmic goiter. Following surgical treatment of the goiter there developed marked swellings of the skin of the face, particularly of the lids, also chemosis and exophthalmos. When thyroidal preparations were administered these symptoms disappeared. The psychic disorders, such as apathy and indifference, which had set in after the operation, disappeared likewise following the administration of thyroidal preparations. The author thinks that the inhibition of the movements of the eyeballs has a mechanical cause, namely, the swelling, for it was secondary, just like the marked impairment of vision, which was caused by the continuous mechanical irritation and by pollution of the cornea by secretions. In discussing the etiology the author expresses the opinion that the manifestations are myxedema symptoms, which is proved by the psychic behavior, by the type of cutaneous swellings and finally by the efficacy of thyroidal preparations. The formation of saclike cutaneous swellings may occur either in hyperthyroidism or in myxedema and can therefore be readily explained in this case. However, it is surprising that the exophthalmos developed after the disappearance of the symptoms of hyperthyroidism

and simultaneously with the myxedema manifestations. It is also pointed out that this exophthalmos with its inhibited motility and with its chemosis differed from that usually observed in hyperthyroidism in that the latter condition there usually is a normal motility of the eyeball and chemosis is absent. For this reason the author assumes that the conditions are probably caused by swellings of the orbital tissues, the existence of which is proved by the chemosis. He concludes that the manifestations in this case are rare ocular symptoms in postoperative myxedema. A review of the literature convinced him that there is no other detailed report of such cases; he found only two similar cares mentioned but detailed clinical histories were not given.

Thyroid psychosis; difficulties in diagnosis. Ingham, S. D. and J. M. Nielson, J. Nerv. & Ment. Dis. **74**: 271. 1931.

From the fact that in each of four cases recovery from the psychosis failed under the usual treatment and was promptly reached by treating the thyroid specifically it is difficult to evade the conclusion that the psychosis was thyrogenous in nature. The presence of a normal metabolic rate does not militate against this interpretation but merely is an added obstacle to be surmounted in making the diagnosis. A knowledge of the most frequent type of psychosis known to occur in thyrotoxicosis does not aid in arriving at a diagnosis in any particular case. Fear and apprehension are classical signs but the cases here presented show that the psychosis may simulate either the manic or the depressed phase of manic-depressive psychosis, dementia precox, delirium, or any toxic psychosis. The clinical signs of loss of weight, fatigue, eye signs, and even thyroid enlargement may be entirely absent in a frank case of thyrotoxicosis. We wish to urge extreme caution in ascribing any psychosis to psychogenic factors without a most thorough search for a source of toxemia. In fact, we doubt whether a frank psychosis ever occurs without at least a chemical disturbance of cerebral function. Two of these four patients with thyrotoxicosis not only tolerated irradiation of the thyroid very well but profited by it, as did none by surgery.—Authors' Summary.

Pathological classification of goiter and its clinical significance. MacCarty, W. C., Ann. Int. Med. **5**: 178. 1931.

The author has attempted to clarify this medley by diagrammatically representing all types of hypertrophic goiters. Of the 32,479 thyroid glands examined, 67% were hypertrophic nodular goiters, 29.3% were hypertrophic parenchymatous goiters, and 2.4% were hypertropic colloid goiters. The anatomic description of the tissue is correlated with clinical findings of each type.
—E. L.

Thyroid function and the Reid Hunt Reaction (Schilddrüsenfunktion und die Reaktion nach Reid Hunt). Paal, H., Arch. f. exper. Path. u. Pharmakol. **148**: 232. 1930. Abst., Physiol. Absts. **15**: 114.

The author gives an interesting description, with photographs of how to remove the thyroid glands from mice by the use of a dissecting (stereoscopic) microscope. He investigated the effect of injections of thyroxin on the aceto-nitrile test in normal mice, confirming previous workers. But in thyroidectomized mice he found no lowered resistance to aceto-nitrile, and the protective action of thyroxin in them was diminished. He investigated also the effect of insulin and choline. Insuline antagonizes the protective action of thyroid.

The calcium and water content of cardiac muscle in hyperthyroidized animals (Sur la teneur en calcium et en eau du muscle cardiaque des animaux hyperthyroidises). Parhon, C. I. and M. Cahane, Compt. rend. Soc. de biol. **106**: 758. 1931.

In three rats and three guinea pigs the calcium was increased and the water very slightly reduced.—J. C. D.

Effect of insulin on the thyroid gland (Wirkt das Insulin auf die Gl. thyreoidea? Vorläufige Mitteilung). Räihä, C. E., Skandin. Arch. f. Physiol. **58**: 8. 1929. Abst., Physiol. Absts. **14**: 513.

A preliminary communication dealing with the appearances found in the thyroids of 4 rabbits that had been used for 2 or 3 years as insulin test ani-

mals. Microscopically, the alveoli were smaller than usual and the cells appeared swollen; where colloid was present it did not stain so deeply. In one gland large irregular follicles were seen with somewhat flattened epithelium and cellular projections into the alveoli.

The cause of exophthalmic goiter; a biochemical hypothesis. Reveno, W. S., Arch. Int. Med. **48**: 592. 1931.

The hypothesis is advanced that exophthalmic goiter is primarily a disturbance resulting from a long-continued toxic process in the intestinal tract. This process not only damages the thyroid gland to the end that varying amounts of its functioning tissue are destroyed, but causes a faulty and irregular metabolism of the amino-acid tyrosine, so that an excess of thyroxine, epinephrine and tyramine is produced. These conclusions are reached in view of (1) the inadequacy of the thyrogenic theory of the disease; (2) the work of McCarrison on the effects of toxic material in the intestinal tract on the thyroid gland; (3) the close relationship between the chemical constitution of thyroxine, epinephrine and tyramine; (4) the common source of these three substances, viz., tyrosine; (5) the changes in the normal tyrosine-tyrosinase reaction and the decarboxylization process for conversion of tyrosine to phenols, with resulting overproduction of the base tyramine, and (6) the pharmacologic action of tyramine.—Author's Summary.

Relation of the thyroid to the spleen (Wechselbeziehungen zwischen Milz und Schilddrüse). Schliephake, E., Arch f. exper. Path. u. Pharmakol. **148**: 1. 1930. Abst., Physiol. Absts. **15**: 114.

The use of blood pressure caused by an intravenous injection of adrenalin and the fall caused by an intravenous injection of choline are altered when the thyroid is removed. The adrenalin effect is reduced, the choline effect is enhanced. The author states that these changes are largely neutralized if the spleen be subsequently removed. If, however, in one of these dogs, which have had first the thyroid and then the spleen removed, an injection of spleen extract be given, then the excessive sensitiveness to choline returns and the adrenalin response diminishes. The spleen extract used was either the expressed juice from fresh minced spleen or a protein-free extract, which retained its activity when heated to 100° or heated for 1 hour at 60°. The extract by itself had no circulatory effect. In normal rabbits preliminary injection of spleen extract increased the fall of blood pressure produced by choline injection.

The heart in hyperthyroidism. Thomas, H. M., Ann. Int. Med. **5**: 184. 1931.

The primary effect of hyperthyroidism on the circulatory system is tachycardia which is due to the increased cellular metabolism of the heart muscle. Congestive heart failure will result if the hyperthyroid tachycardia persists in an older individual. Young, healthy hearts are not prone to fibrillation due to the severe work imposed upon them by hyperthyroidism. The fibrillating heart is best controlled by digitalis. There are no pronounced pathological lesions produced in the heart by hyperthyroidism so that relief from hyperthyroidism allows the heart to regain its pre-hyperthyroid condition.—E. L.

Action of thyroid on spleen and blood volume (Die Schilddrüse als ein Regulator der kreisenden Blutmenge und ihre Wirkung auf das Blutdepot der Milz). Wislicki, L., Ztschr. f. d. ges. exper. Med. **71**: 696. 1930. Abst., Physiol. Absts. **16**: 266.

Estimations of the blood volume by the trypan-red injection method and of relative volumes of cells and plasma were made on patients suffering from Graves' disease. There is an increase in the blood volume due to increase in the plasma and in the red-cell volume. This is reduced by treatment with iodine and by thyroidectomy. Administration of thyroid to myxoedematous subjects caused an increase in the blood volume. Normal and thyroidectomized rabbits were exposed to CO (a) at rest, and (b) with muscular exercise. It was found that in the rabbits without thyroids there was no increase in the CO content of the splenic blood as a result of the exercise, such as was found in the normals. After administration of thyroid, exercise had the usual effect in increasing the splenic blood CO content. The conclusion is drawn that the increased metabolism following thyroid excess leads to an emptying of the blood depots of the body.